**Table 6_12.1** **In vitro percutaneous absorption of tolylfluanid as an ingredient of Euparen M 50 WG through human and rat epidermal membranes (mean values)**

| **Applied amount of $^{14}$C-Tolylfluanid [mg/cm² of skin]** | **1.707 (≈15% Euparen M 50 WG)** | | | | **0.082 (≈1.5% Euparen M 50 WG)** | | | | **0.0073 (≈0.15% Euparen M 50 WG)** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Radioactivity absorbed | of applied dose [%] | | amount [µg/cm²] | | of applied dose [%] | | amount [µg/cm²] | | of applied dose [%] | | amount [µg/cm²] | |
| | Human [n=1*] | Rat [n=4] | Human [n=1*] | Rat [n=4] | Human [n=1*] | Rat [n=3] | Human [n=1*] | Rat [n=3] | Human [n=1*] | Rat [n=4] | Human [n=1*] | Rat [n=4] |
| Time of exposure [h] | | | | | | | | | | | | |
| 8 | | | | | | | | | | | | |
| 24 | | | | | | | | | | | | |
| Flux [µg/cm²/h] | | | | | | | | | | | | |
| Recovery [% of applied dose] | | | | | | | | | | | | |

* 4-fold determination

**Table 6_12.2** **In vitro percutaneous absorption of tolylfluanid as pure substance through human and rat epidermal membranes (mean values)**

| **Applied amount of $^{14}$C-Tolylfluanid [mg/cm² of skin]** | **0.638** | | | | **0.071** | | | | **0.0068** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Radioactivity absorbed | of applied dose [%] | | amount [µg/cm²] | | of applied dose [%] | | amount [µg/cm²] | | of applied dose [%] | | amount [µg/cm²] | |
| | Human [n=1*] | Rat [n=4] | Human [n=1*] | Rat [n=4] | Human [n=1*] | Rat [n=4] | Human [n=1*] | Rat [n=3] | Human [n=1*] | Rat [n=4] | Human [n=1*] | Rat [n=4] |
| Time of exposure [h] | | | | | | | | | | | | |
| 8 | | | | | | | | | | | | |
| 24 | | | | | | | | | | | | |
| Flux [µg/cm²/h] | | | | | | | | | | | | |
| Recovery [% of applied dose] | | | | | | | | | | | | |

* 4-fold determination

## Section A6.3.1 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.1 Subacute oral toxicity test on rats

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted]. (1988): KUE 13183 B (Tolylfluanid, Euparen M active ingredient) - Subacute toxicological study on the question of an effect on the thyroid in rats (Four week feeding test). [redacted] 1988-09-28.

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study**

The study was not performed using any official guidelines for test methods. The experiment was carried out according to a specific study plan in order to examine the effects of tolylfluanid on the function of the thyroid in rats.

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

### 3 MATERIALS AND METHODS

The experiment was carried out according to a specific study plan in order to examine the effects of tolylfluanid on the function of the thyroid in rats.

Groups of 10 male and 10 female Wistar (Bor: WISW SPF-Cpb) rats were dosed with tolylfluanid [redacted] for four weeks. [redacted] X

**Section A6.3.1** **Repeated dose Toxicity**

**Annex Point IIA6.3** 6.3.1 Subacute oral toxicity test on rats

## 4 RESULTS AND DISCUSSION

[redacted]

## 5 CONCLUSION

**5.1 Conclusion**

Functional disturbance of the thyroid glands, demonstrated as consistently lowered levels of T4, a less pronounced reduction in T3, and corresponding increases in TSH levels, were observed mainly at the high dose level of 7500 ppm. A decrease in T4 levels was observed also in 1500 ppm males at the end of the study. Necropsies showed a paleness of the thyroids in high dose animals, but no histopathological changes were observed. The relative kidney weights were increased in both sexes at 7500 ppm. The NOAEL, based on increased kidney weights and changes in levels of thyroidal hormones, was 1500 ppm in females and 300 ppm in males.

5.1.1 Reliability [redacted]

## Section A6.3.1 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.1 Subacute oral toxicity test on rats

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 23, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.3.2 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute dermal toxicity test on rabbits

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted]. (1995), KUE 13183 B - Subacute dermal toxicity study on rabbits
[redacted] 1995-02-06 (unpublished).

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** [redacted]

OECD guideline 410, EU-guideline 67/548/EEC, Annex V, B.9

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

### 3 MATERIALS AND METHODS

Male and female adult New Zealand (HC:NZW) rabbits were treated with tolylfluanid ([redacted] dermally [redacted]

[redacted]

### 4 RESULTS AND DISCUSSION

[redacted]

## Section A6.3.2 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute dermal toxicity test on rabbits

[redacted]

**5 CONCLUSION**

**5.1 Conclusion**

[redacted]

| | | |
|---|---|---|
| 5.1.1 | LO(A)EL | Systemic LOEL > 300 mg/kg<br>Local LOAEL ≤ 1 mg/kg |
| 5.1.2 | NO(A)EL | Systemic NOEL ≥ 300 mg/kg<br>Local NOAEL < 1 mg/kg |
| 5.1.3 | Other | — |
| 5.1.4 | Reliability | [redacted] |

## Section A6.3.2 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute dermal toxicity test on rabbits

| Evaluation by Competent Authorities | |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 24, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.3.2 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.2 Subacute dermal toxicity test on rabbit (1)

Official use only

### 1 REFERENCE

**1.1 Reference** [redacted] (1971): Methyl-Euparen – Subacute cutaneous application to rabbits. [redacted] 1971-03-05.

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** No

**2.2 GLP** [redacted]

**2.3 Deviations** -

### 3 MATERIALS AND METHODS

Five male and five female adult Mount Vizcacha strain rabbits were treated with "technical grade methyl-Euparen" ([redacted]

[redacted]

### 4 RESULTS AND DISCUSSION

[redacted]

## Section A6.3.2 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.2 Subacute dermal toxicity test on rabbit (1)

### 5 CONCLUSION

**5.1 Conclusion** [redacted]

5.1.1 LO(A)EL

5.1.2 NO(A)EL NOAEL = 500 mg/kg

5.1.3 Other —

5.1.4 Reliability [redacted]

## Section A6.3.2 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.2 Subacute dermal toxicity test on rabbit (1)

| Evaluation by Competent Authorities | |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 24, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted] (2002a) KUE 13183 B Subacute inhalation toxicity on rats ([redacted] 2002-02-20 (unpublished).

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** [redacted]

OECD guideline 412, EU-guideline 67/548/EEC, Annex V, B.8

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

### 3 MATERIALS AND METHODS

The purpose of the study was to investigate the subacute inhalation toxicity in rats after repeated exposure to different substance concentrations of a not micronised dust. [redacted]

For a series of dynamic inhalation tests, groups of 10 male and 10 female Wistar rats (approx. 170-240 g) were simultaneously exposed nose-only [redacted]

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats

[redacted]

**4 RESULTS AND DISCUSSION**

[redacted]

**Section A6.3.3** **Repeated dose Toxicity**

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats

[redacted]

## 5 CONCLUSION

**5.1 Conclusion**

[redacted]

| | | |
|---|---|---|
| 5.1.1 | LO(A)EL | 0.004 mg/L |
| 5.1.2 | NO(A)EL | 0.001 mg/L |
| 5.1.3 | Other | — |
| 5.1.4 | Reliability | 1 |

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats

| Evaluation by Competent Authorities | |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 25, 2008 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| | [redacted] |
| | [redacted] |
| | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Table A6_3-1. Subacute inhalation toxicity in male and female rats [redacted]**

| Dose [mg/ L] | Result* | Onset and duration of non-histopathological effects |
|---|---|---|
| | males | |
| 0<br>0.001<br>0.004<br>0.011 | [redacted] | [redacted] |
| | females | |
| 0<br>0.001<br>0.004<br>0.011 | [redacted] | [redacted] |

* number of dead animals / animals with signs of toxicity / animals in the group;
d = day; 0d = first day of exposure; + = substance related histopathological findings

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (1)

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted] (1967): KUE 13183 B – Toxicological studies on the active ingredient [redacted] 1967-05-17.

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** No

**2.2 GLP** [redacted]

**2.3 Deviations** -

### 3 MATERIALS AND METHODS

The purpose of the study was to investigate the subacute inhalation toxicity in rats after a single exposure to different substance concentrations under repeated inhalation exposure conditions.

[redacted]

### 4 RESULTS AND DISCUSSION

[redacted]

### 5 CONCLUSION

**5.1 Conclusion** [redacted]

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (1)

[redacted]

| | | |
|---|---|---|
| 5.1.1 | LO(A)EL | ≥ 0.032 mg/L |
| 5.1.2 | NO(A)EL | 0.017 mg/L |
| 5.1.3 | Other | — |
| 5.1.4 | Reliability | [redacted] |

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (1)

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 25, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Table 6_3_3.1 Repeated inhalation toxicity in male rats**

| Exposure concentration analytically determined [mg/L] | Duration of exposure [hour] | Results* |
|---|---|---|
| 0.017<br>0.032<br>0.145 | [redacted] | [redacted] |

* number of dead animals / animals with signs of toxicity / animals in the group

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (2)

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted] (1996): KUE 13183B (common name: Tolylfluanid) - Pilot-Study on subacute inhalation toxicity in rats (5x6 hours exposition). [redacted], 1996-09-18.

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study**

The method complied, besides exposure's duration, with OECD guideline 412 or EU-guideline 67/548/EEC, Annex V, B.8.

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

### 3 MATERIALS AND METHODS

The purpose of the pilot study was to investigate the subacute inhalation toxicity in rats after repeated exposure to different substance concentrations of a respirable (micronised) dust.

For a series of dynamic inhalation tests, groups of 10 male and 10 female Wistar rats (approx. 170-220 g) were simultaneously exposed nose-only [redacted]

**Section A6.3.3** **Repeated dose Toxicity**

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (2)

[redacted]

4 **RESULTS AND DISCUSSION**

[redacted]

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (2)

## 5 CONCLUSION

**5.1 Conclusion** [redacted]

5.1.1 LO(A)EL

5.1.2 NO(A)EL 0.014 mg/L

5.1.3 Other —

5.1.4 Reliability [redacted]

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (2)

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 25, 2008 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| | [redacted] |
| **Remarks** | [redacted] |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Table 6_3_3.1 Subacute inhalation toxicity in male and female rats exposed 5 x 6h to micronised substance**

| Dose [mg/ L] | Result* | Onset and duration of effects | Onset of death |
|---|---|---|---|
| males | | | |
| 0<br>0.0016<br>0.014<br>0.124 |  |  |  |
| females | | | |
| 0<br>0.0016<br>0.014<br>0.124 |  |  |  |

* number of dead animals / animals with signs of toxicity / animals in the group;
d = day; 0d = first day of exposure

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (3)

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted]1997): KUE 13183 B (common name: Tolylfluanid) - Study on subacute inhalation toxicity in rats (20 x 6 hours exposure) according to OECD-Guideline No. 412. [redacted] 1997-01-20.

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** [redacted]

OECD guideline 412 or EU-guideline 67/548/EEC, Annex V, B.8.

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

### 3 MATERIALS AND METHODS

The purpose of the study was to investigate the subacute inhalation toxicity in rats after repeated exposure to different substance concentrations of a respirable (micronised) dust.

For a series of dynamic inhalation tests, groups of 10 male and 10 female Wistar rats (approx. 170-240 g) were simultaneously exposed nose-only [redacted]

**Section A6.3.3** **Repeated dose Toxicity**

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (3)

[redacted]

**4 RESULTS AND DISCUSSION**

[redacted]

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (3)

[redacted]

## 5 CONCLUSION

### 5.1 Conclusion

[redacted]

5.1.1 LO(A)EL

5.1.2 NO(A)EL 0.0015 mg/L

5.1.3 Other —

5.1.4 Reliability [redacted]

## Section A6.3.3 Repeated dose Toxicity

**Annex Point IIA6.3** 6.3.3 Subacute inhalation toxicity test on rats (3)

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 25, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Table 6_3_3.1 Subacute inhalation toxicity in male and female rats exposed 20 x 6h to micronised substance**

| Dose [mg/ L] | Result* | Onset and duration of effects | Onset of death |
|---|---|---|---|
| Males | | | |
| 0<br>0.0002<br>0.0015<br>0.0098<br>0.05** |  |  |  |
| Females | | | |
| 0<br>0.0002<br>0.0015<br>0.0098<br>0.05** |  |  |  |

* number of dead animals / animals with signs of toxicity / animals in the group;
** treatment terminated after two weeks; d: day; 0d: first day of exposure

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on dogs

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted] (1974), KUE 13183b (Tolylfluanid / Euparen M®) - Subchronic toxicity study on dogs (thirteen-week feeding experiment).
[redacted] 1974-09-12 ([redacted]
[redacted]

**1.2 Data protection**

[redacted]

1.2.1 Data owner

[redacted]

1.2.2 Companies with letter of access

[redacted]

1.2.3 Criteria for data protection

[redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study**

The study was conducted broadly in accordance with OECD Guideline 409 and the subchronic toxicity study guideline described in Directive 92/69/EEC.

**2.2 GLP**

[redacted]

**2.3 Deviations**

[redacted]

### 3 MATERIALS AND METHODS

Groups of 4 male and 4 female Beagle dogs were dosed with tolylfluanid via the diet [redacted]

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on dogs

### 4 RESULTS AND DISCUSSION

[redacted]

### 5 CONCLUSION

**5.1 Conclusion**

[redacted]. The NOAEL in the study is 1000 ppm, based on clinical signs, effects on body weight development and increased liver and thyroid weights observed at the highest dose of 3000 ppm.

| | | |
|---|---|---|
| 5.1.1 | LO(A)EL | 3000 ppm (93-99 mg /kg/day) |
| 5.1.2 | NO(A)EL | 1000 ppm (33-34 mg /kg/day) |
| 5.1.3 | Other | — |
| 5.1.4 | Reliability | [redacted] |

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on dogs

| Evaluation by Competent Authorities | |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 26, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | [redacted] |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on rats

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted] (1995), KUE 13183B (c.n. Tolylfluanid) - Subchronic toxicity study in Wistar rats, [redacted] 1995-09-27, amended: 2000-10-04 (unpublished)

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** [redacted]

FIFRA 82-1, 67/548/EEC, OECD no. 408, MAFF requirements – Japan 1985

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

### 3 MATERIALS AND METHODS

Groups of 10 male and 10 female Wistar (Hsd/Win:WU) rats were dosed with tolylfluanid via the diet [redacted]

[redacted]

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on rats

[redacted]

**4 RESULTS AND DISCUSSION**

[redacted]

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on rats

[redacted]

## 5 CONCLUSION

**5.1 Conclusion**

[redacted]

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on rats

[redacted]

| | | |
|---|---|---|
| 5.1.1 | LO(A)EL | 1650 ppm (108 mg/kg bw/day) |
| 5.1.2 | NO(A)EL | 300 ppm (20 mg/kg bw/day) |
| 5.1.3 | Other | — |
| 5.1.4 | Reliability | [redacted] |

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on rats

| Evaluation by Competent Authorities | |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 26, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on rats (1)

Official use only

### 1 REFERENCE

**1.1 Reference** [redacted] (1976): KUE 13183B – Subchronic toxicological experiments on rats (feeding experiment over 3 months). [redacted], 1976-02-20.

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** The study was not performed using any official guidelines for test methods. The experiment complies only partly with OECD Guideline 408

**2.2 GLP** [redacted]

**2.3 Deviations** -

### 3 MATERIALS AND METHODS

Groups of 15 male and 15 female Wistar (SPF) rats were dosed with tolylfluanid (technical active substance, purity given as [redacted] via the diet at concentrations of 150, 500, 1500 or 4500 ppm for three months.

[redacted]

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on rats (1)

### 4 RESULTS AND DISCUSSION

[redacted]

### 5 CONCLUSION

**5.1 Conclusion**

[redacted]

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on rats (1)

| | | |
|---|---|---|
| 5.1.1 | LO(A)EL | 500 ppm (approximately 60 mg/kg bw/day) |
| 5.1.2 | NO(A)EL | 150 ppm (approximately 18 mg/kg bw/day) |
| 5.1.3 | Other | — |
| 5.1.4 | Reliability | [redacted] |

## Section A6.4.1 Subchronic Toxicity

**Annex Point IIA6.4** 6.4.1 Subchronic oral toxicity test on rats (1)

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 26, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** *(specify)* |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

| | | |
|---|---|---|
| **Section 6.4.2-6.4.3**<br>**Annex Point IIA 6.4** | **Subchronic dermal and inhalation toxicity** | |
| | **JUSTIFICATION FOR NON-SUBMISSION OF DATA** | Official use only |
| **Other existing data [...]** | **Technically not feasible [ ]** **Scientifically unjustified [X]** | |
| **Limited exposure [X]** | **Other justification [ ]** | |
| **Detailed justification:** | Subacute toxicity testing in rats has been performed by dermal and inhalation exposure. Further subchronic testing by these routes is deemed unnecessary for the following reasons:<br>Tolylfluanid possesses a very low vapour pressure. Exposure to Tolylfluanid vapours is therefore limited. Spray applications are not intended for Tolylfluanid-containing wood preservatives. This envisaged pattern of use minimizes exposure to aerosols.<br>Submission of subchronic dermal toxicity studies is only necessary if route-to route extrapolation is not possible. Subacute tests demonstrate that this is not the case.<br>Both dermal and inhalation route subacute toxicity studies are submitted. It is therefore justified to submit no data on subchronic toxicity with regard to the dermal and inhalation route. | |
| **Undertaking of intended data submission [ ]** | – | |
| | **Evaluation by Competent Authorities** | |
| | *Use separate "evaluation boxes" to provide transparency as to the comments and views submitted* | |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** | |
| **Date** | October 28, 2005 | |
| **Evaluation of applicant's justification** | [redacted] | |
| **Conclusion** | [redacted] | |
| **Remarks** | | |
| | **COMMENTS FROM OTHER MEMBER STATE** *(specify)* | |
| **Date** | *Give date of comments submitted* | |
| **Evaluation of applicant's justification** | *Discuss if deviating from view of rapporteur member state* | |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* | |
| **Remarks** | | |

**Section A6.5/6.7** **Chronic Toxicity / Carcinogenicity**

**Annex Point IIA6.5/6.7** 6.5/6.7 Chronic toxicity and carcinogenicity in rats

Official use only

## 1 REFERENCE

**1.1 Reference**

[redacted]. (1996) KUE 13183b (c.n. Tolylfluanid) - Study on Chronic Toxicity and Carcinogenicity in Wistar rats (administration in food over 2 years). [redacted] 1996-09-13, Amended: 2000-10-04 (unpublished)

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

## 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** [redacted]

OECD guideline 453 (Directive 67/548/EEC, Annex V, Method B.33), FIFRA §83-5, Society of Agricultural Chemicals, Japan 1985 (MAFF)

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

## 3 MATERIALS AND METHODS

Groups including 50 male and 50 female Wistar (Bor: WISW SPF-Cpb) rats were dosed with tolylfluanid [redacted]%) via the diet at concentrations of 60, 300, 1500 and 7500 ppm for 105 weeks. [redacted]

[redacted]

**Section A6.5/6.7** **Chronic Toxicity / Carcinogenicity**

**Annex Point IIA6.5/6.7** 6.5/6.7 Chronic toxicity and carcinogenicity in rats

[redacted]

**4 RESULTS AND DISCUSSION**

[redacted]

**Section A6.5/6.7**

**Annex Point IIA6.5/6.7**

## Chronic Toxicity / Carcinogenicity

6.5/6.7 Chronic toxicity and carcinogenicity in rats

**Section A6.5/6.7** **Chronic Toxicity / Carcinogenicity**

**Annex Point IIA6.5/6.7** 6.5/6.7 Chronic toxicity and carcinogenicity in rats

[redacted]

## 5 CONCLUSION

### 5.1 Conclusion

[redacted] The overall NOEL for tolylfluanid in the study is 300 ppm, corresponding to an intake of 18 – 21 mg tolylfluanid/kg bw/day, based on treatment-related changes in the osseous parts of the musculo-skeletal system at 1500 ppm and 7500 ppm.

5.1.1 Reliability [redacted]

## Section A6.5/6.7

**Annex Point IIA6.5/6.7**

## Chronic Toxicity / Carcinogenicity

6.5/6.7 Chronic toxicity and carcinogenicity in rats

| Evaluation by Competent Authorities | |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 26, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Table A6_5-1 Cumulative mortality of animals in the main groups and satellite groups at intervals of 90 days from the start of the study to the last necropsy**

| Mortality – main groups | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose (ppm) | 0 | 60 | 300 | 1500 | 7500 | 0 | 60 | 300 | 1500 | 7500 |
| Sex | m | m | m | m | m | f | f | f | f | f |
| No. of animals | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Days | | | | | | | | | | |
| 1-90 | | | | | | | | | | |
| 1-180 | | | | | | | | | | |
| 1-270 | | | | | | | | | | |
| 1-360 | | | | | | | | | | |
| 1-450 | | | | | | | | | | |
| 1-540 | | | | | | | | | | |
| 1-630 | | | | | | | | | | |
| 1-720 | | | | | | | | | | |
| 1-751 | | | | | | | | | | |
| % | | | | | | | | | | |
| Mortality – satellite groups | | | | | | | | | | |
| No. of animals | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Days | | | | | | | | | | |
| 1-90 | | | | | | | | | | |
| 1-180 | | | | | | | | | | |
| 1-270 | | | | | | | | | | |
| 1-360 | | | | | | | | | | |
| 1-367 | | | | | | | | | | |
| % | | | | | | | | | | |

m= male, f = female

**Table A6_5-2 Incidences of gross pathological findings in main study groups (all animals)**

| **Incidence of gross pathological findings in main groups** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose (ppm)** | **0** | **60** | **300** | **1500** | **7500** | **0** | **60** | **300** | **1500** | **7500** |
| **Sex** | **m** | **m** | **m** | **m** | **m** | **f** | **f** | **f** | **f** | **f** |
| No. of animals | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Skull discoloration | | | | | | | | | | |
| Teeth discoloration | | | | | | | | | | |

m= male, f = female

**Table A6_5-3 Conspicuous non-neoplastic findings in satellite groups and main study groups**

| **Dose (ppm)** | **0** | **60** | **300** | **1500** | **7500** | **0** | **60** | **300** | **1500** | **7500** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Sex** | **m** | **m** | **m** | **m** | **m** | **f** | **f** | **f** | **f** | **f** |
| Satellite groups | | | | | | | | | | |
| SKULLCAP | | | | | | | | | | |
| Altered bone matrix | | | | | | | | | | |
| Focal hyperostosis | | | | | | | | | | |
| THYROID | | | | | | | | | | |
| Follicular mineralisation | | | | | | | | | | |
| TESTES | | | | | | | | | | |
| Leydig cell hyperplasia | | | | | | | | | | |

| Dose (ppm) Sex | 0 m | 60 m | 300 m | 1500 m | 7500 m | 0 f | 60 f | 300 f | 1500 f | 7500 f |
|---|---|---|---|---|---|---|---|---|---|---|
| LIVER Hypertrophy of hepatocytes | | | | | | | | | | |
| Main study groups | | | | | | | | | | |
| LIVER Cytoplasmic change, portal | | | | | | | | | | |
| Cytoplasmic change, focal | | | | | | | | | | |
| Hepatocellular alteration | | | | | | | | | | |
| Hepatocellular vacuolation | | | | | | | | | | |
| Focal fatty change | | | | | | | | | | |
| Clear cell focus/foci | | | | | | | | | | |
| STERNUM Osteopetrosis | | | | | | | | | | |
| SKULLCAP Focal hyperostosis | | | | | | | | | | |
| NASAL CAVITIES Osseus thickening | | | | | | | | | | |
| KIDNEYS Tubular pigment deposition | | | | | | | | | | |
| Papillary mineralisation | | | | | | | | | | |
| TESTES Leydig cell hyperplasia | | | | | | | | | | |
| THYROID GLAND Follicular cell hyperplasia | | | | | | | | | | |
| ADRENAL GLANDS Medullary hyperplasia | | | | | | | | | | |
| LUNG Alveolar histiocytosis | | | | | | | | | | |

m= male, f = female

**Table A6_5-4 Neoplastic findings in the thyroid gland and female reproductive system**

| Incidence of neoplasms | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose (ppm)**<br>**Sex** | **0**<br>**m** | **60**<br>**m** | **300**<br>**m** | **1500**<br>**m** | **7500**<br>**m** | **0**<br>**f** | **60**<br>**f** | **300**<br>**f** | **1500**<br>**f** | **7500**<br>**f** |
| THYROID GLAND | | | | | | | | | | |
| Carcinoma/follicular(m) | | | | | | | | | | |
| Adenoma/follicular (b) | | | | | | | | | | |
| Tumor/C-cell (m) | | | | | | | | | | |
| Tumor/C-cell (b) | | | | | | | | | | |
| UTERUS | | | | | | | | | | |
| Carcinoma/squam. cell (m) | | | | | | | | | | |
| Keratoacanthoma (b) | | | | | | | | | | |
| Schwannoma (m) | | | | | | | | | | |
| Schwannoma (b) | | | | | | | | | | |
| Leiomyoma (b) | | | | | | | | | | |
| Adenocarcinoma (m) | | | | | | | | | | |
| Adenoma (b) | | | | | | | | | | |
| Stromal polyps (b) | | | | | | | | | | |
| Stromal sarcoma (m) | | | | | | | | | | |
| Glandular polyps (b) | | | | | | | | | | |
| Granular cell tumor (b) | | | | | | | | | | |
| VAGINA | | | | | | | | | | |
| Papilloma (b) | | | | | | | | | | |
| Granular cell tumor (b) | | | | | | | | | | |
| CLITORAL GLANDS | | | | | | | | | | |
| Adenocarcinoma (m) | | | | | | | | | | |

(m) = malignant, (b) = benign

**Table A6_5-5 Total incidence of neoplastic findings in the main study groups**

| Incidence of neoplasms in main groups (including intercurrent deaths) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose (ppm)**<br>**Sex** | **0**<br>**m** | **60**<br>**m** | **300**<br>**m** | **1500**<br>**m** | **7500**<br>**m** | **0**<br>**f** | **60**<br>**f** | **300**<br>**f** | **1500**<br>**f** | **7500**<br>**f** |
| No. of animals examined | | | | | | | | | | |
| Animals with neoplasms | | | | | | | | | | |
| Animals with exclusively benign neoplasms | | | | | | | | | | |
| Animals with exclusively malignant neoplasms | | | | | | | | | | |
| Animals with benign and malignant neoplasms | | | | | | | | | | |
| Animals with metastasizing neoplasms | | | | | | | | | | |
| Total number of neoplasms | | | | | | | | | | |

**Section A6.5/6.7** **Chronic Toxicity / Carcinogenicity**

**Annex Point IIA6.5/6.7** 6.5/6.7 Chronic toxicity and carcinogenicity in rats (1)

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## 1 REFERENCE

**1.1 Reference**

[redacted] (1982): KUE 13183 B (Tolylfluanid, active substance in Euparen M) - Chronic toxicological investigations on rats. [redacted], 1982-06-30.

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

## 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** The test method referred to is an in-house method.

**2.2 GLP** [redacted]

**2.3 Deviations** -

## 3 MATERIALS AND METHODS

[redacted]

[redacted]

## 4 RESULTS AND DISCUSSION

[redacted]

**Section A6.5/6.7** **Chronic Toxicity / Carcinogenicity**

**Annex Point IIA6.5/6.7** 6.5/6.7 Chronic toxicity and carcinogenicity in rats (1)

[redacted]

## 5 CONCLUSION

### 5.1 Conclusion

[redacted]

The NOAEL of the study is 300 ppm (20 mg/kg bw/day), based on bone alterations due to the increased intake of fluoride delivered by tolylfluanid administration.

5.1.1 Reliability [redacted]

## Section A6.5/6.7 Chronic Toxicity / Carcinogenicity

**Annex Point IIA6.5/6.7** 6.5/6.7 Chronic toxicity and carcinogenicity in rats (1)

| Evaluation by Competent Authorities | |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 29, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| | [redacted] |
| | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Table 6_5.1 Unscheduled deaths during the experiment**

| | Group/Dose level (ppm tolylfluanid) | | | |
|---|---|---|---|---|
| | 0 | 300 | 1500 | 7500 |
| Males | [redacted] | [redacted] | [redacted] | [redacted] |
| Females | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 6_5.2 Neoplastic findings (blastomas) in rat**

| Organ/neoplasia | Male rats | | | | Female rats | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 ppm | 300 ppm | 1500 ppm | 7500 ppm | 0 ppm | 300 ppm | 1500 ppm | 7500 ppm |
| Abdominal cavity | | | | | | | | |
| Liposarcoma (m) | | | 1 | | | | | |
| Non-classifiable sarcoma (m) | | | | | | | 1 | |
| Connective tissue | | | | | | | | |
| Malignant fibrous histiocytoma (m) | | 1 | | 1 | | 1 | 1 | |
| Brain | | | | | | | | |
| Glioma (b) | | | 1 | | | | | |
| Meningioma (b) | 1 | | | 1 | | | 1 | |
| Skin | | | | | | | | |
| Fibrosarcoma (m) | | 1 | | | | | | |
| Squamous epithelial carcinoma (m) | | | | | | | | |
| Pituitary | | | | | | | | |
| Adenoma (b) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Carcinoma (m) | | | | | | | 1 | |
| Bone | | | | | | | | |
| Osteosarcoma (m) | 1 | | | | | | | |
| Carcinoma (m) | | | 1 | | | | | |
| Liver | | | | | | | | |
| Carcinoma (m) | | | | | | | | |
| Malignant fibrous histicytoma (m) | | | | | | | | |
| Mamma | | | | | | | | |
| Fibroadenoma (b) | | | | | | 1 | 1 | 1 |
| Adenoma (b) | | | | | | | | |
| Carcinoma (m) | | | | | | | 1 | |
| Mediastinum | | | | | | | | |
| Scirrhous thymus carcinoma (m) | | 1 | | | | | | |
| Adrenals | | | | | | | | |
| Cortical adenoma (b) | | 1 | | | 1 | | | |
| Phaeochromocytoma (b) | 1 | | 1 | 1 | | | | |
| Cortical carcinoma (m) | | | | 1 | | | | |
| Kidneys | | | | | | | | |
| Lipomatous blastoma (n.c.) | | 1 | | 1 | | | | |
| Ovaries | | | | | | | | |
| Granulosa theca cell blastoma (b) | | | | | 1 | 1 | 1 | 1 |
| Papilloma (b) | | | | | | | | |
| Pancreas | | | | | | | | |
| Islet cell adenomas (b) | | 1 | | | | | | |
| Pancreas adenoma (b) | 1 | | | | | | | |
| Reticulohistiocytary system | | | | | | | | |
| Lymphoma (m) | 1 | | 1 | | 1 | 1 | | |
| Thyroid | | | | | | | | |
| C-cell adenoma (b) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Cystic papillar adenoma (b) | | | | | | | | |
| Follicular adenoma (b) | | | | 1 | | | | 1 |
| Follicular carcinoma (m) | | | | 1 | | | | 1 |
| Testes | | | | | | | | |
| Leydig cell adenoma (b) | 1 | 1 | 1 | 1 | | | | |
| Mesothelioma (b) | | | | | | | | |
| Subcutis | | | | | | | | |
| Liposarcoma (m) | | | | | | 1 | | |
| Fibrosarcoma (m) | 1 | | 1 | | | | | |
| Fibroma (b) | 1 | | | | | | | 1 |

Numbers of malignant tumors are presented in brackets (), b = benign, m = malignant, nc = not classified

Table 6_5.2 continued on the next page

**Table 6_5.2 (continued) Neoplastic findings (blastomas) in rat**

| Organ/neoplasia | Male rats | | | | Female rats | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 ppm | 300 ppm | 1500 ppm | 7500 ppm | 0 ppm | 300 ppm | 1500 ppm | 7500 ppm |
| Uterus | | | | | | | | |
| Carcinoma (m) | | | | | | | | |
| Adenomatous polyp (b) | | | | | | | | |
| Leiomyosarcoma (m) | | | | | | | | |
| Endometrial stromapolyp (b) | | | | | | | | |
| Endometrial stromasarcoma (m) | | | | | | | | |
| Not classified | | | | | | | | |
| Vagina | | | | | | | | |
| Squamous epithelium carcinoma (m) | | | | | | | | |
| Not assigned | | | | | | | | |
| Not classified | | | | | | | | |

**Numbers of malignant tumors are presented in brackets (), b = benign, m = malignant, nc = not classified**

**Table 6_5.3 Numbers of blastoma hosts in the examined groups. The numbers in brackets are the percentages of the total number of examined animals**

| | Male rats | | | | Female rats | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 ppm | 300 ppm | 1500 ppm | 7500 ppm | 0 ppm | 300 ppm | 1500 ppm | 7500 ppm |
| Number of examined animals | | | | | | | | |
| Number of blastoma hosts | | | | | | | | |
| Animals with benign blastomas | | | | | | | | |
| Animals with malignant blastomas | | | | | | | | |
| Animals with benign and malignant blastomas | | | | | | | | |
| Animals with non-classifiable blastomas | | | | | | | | |

**Table 6_5.4** **Numbers of females with blastomas of the uterus after histopathological analysis of all female controls. The numbers in brackets are the percentages of the total number of examined animals**

| Dose | 0 ppm | 300 ppm | 1500 ppm | 7500 ppm |
|---|---|---|---|---|
| Number of examined animals | 100 | 50 | 50 | 50 |
| Uterus | | | | |
| Carcinoma (m) | [redacted] | [redacted] | [redacted] | [redacted] |
| Leiomyosarcoma (m) | [redacted] | | | [redacted] |
| Adenomatous polyp (b) | [redacted] | | | [redacted] |
| Endometrial stromapolyp (b) | [redacted] | [redacted] | [redacted] | [redacted] |

(b) = benign, (m) = malignant

## Section A6.5

**Annex Point IIA6.5**

## Chronic Toxicity / Carcinogenicity

6.5 Chronic toxicity in dogs (1)

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted] (1986): KUE 13183 B (common name: Tolylfluanid) - Chronic toxicity to dogs after oral administration (Twelve-month capsule study). [redacted], 1986-07-22.

[redacted]

**1.2 Data protection**

[redacted]

1.2.1 Data owner

[redacted]

1.2.2 Companies with letter of access

[redacted]

1.2.3 Criteria for data protection

[redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study**

The experiment was done as an in-house method, since no appropriate guideline for subchronic toxicity testing in non-rodents was available at the time of the study.

**2.2 GLP**

[redacted]

**2.3 Deviations**

-

### 3 MATERIALS AND METHODS

Groups of 4 male and 4 female Beagle dogs were dosed daily with tolylfluanid in gelatin capsules, starting with three dose levels: 2.5, 12.5 or 62.5 mg/kg bw/day. [redacted]

**Section A6.5** **Chronic Toxicity / Carcinogenicity**

**Annex Point IIA6.5** 6.5 Chronic toxicity in dogs (1)

[redacted]

**4 RESULTS AND DISCUSSION**

[redacted]

**Section A6.5** **Chronic Toxicity / Carcinogenicity**

**Annex Point IIA6.5** 6.5 Chronic toxicity in dogs (1)

[redacted]

## 5 CONCLUSION

**5.1 Conclusion**

[redacted] The NOAEL in the study is 12.5 mg/kg bw/day based on body weight gain reduction, liver enzyme level alterations and kidney effects at 62.5-125 mg/kg bw/day.

5.1.1 Reliability [redacted]

## Section A6.5 Chronic Toxicity / Carcinogenicity

**Annex Point IIA6.5** 6.5 Chronic toxicity in dogs (1)

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 30, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| | [redacted] |
| | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.5 Chronic Toxicity / Carcinogenicity

**Annex Point IIA6.5**

6.5 Chronic toxicity in dogs (2)

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted] (1997): KUE 13183 B (c.n. Tolylfluanid) - Chronic (52 week) Oral Toxicity Study in Dogs (Study No. T6060604), [redacted], 1997-09-24, amended 1998-09-17 (unpublished).

[redacted]

**1.2 Data protection**

[redacted]

1.2.1 Data owner

[redacted]

1.2.2 Companies with letter of access

[redacted]

1.2.3 Criteria for data protection

[redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study**

[redacted]

OECD 452

**2.2 GLP**

[redacted]

**2.3 Deviations**

-

### 3 MATERIALS AND METHODS

Groups of 4 male and 4 female Beagle dogs were dosed daily with tolylfluanid in gelatine capsules at dose levels of 0, 5, 20 or 80 mg/kg bw/day for a minimum of 364 days. [redacted]

**Section A6.5** **Chronic Toxicity / Carcinogenicity**

**Annex Point IIA6.5** 6.5 Chronic toxicity in dogs (2)

[redacted]

## 4 RESULTS AND DISCUSSION

[redacted]

## 5 CONCLUSION

**5.1 Conclusion**

[redacted]

**Section A6.5** **Chronic Toxicity / Carcinogenicity**

**Annex Point IIA6.5** 6.5 Chronic toxicity in dogs (2)

[redacted]. The NOAEL of the study is 80 mg/kg bw/day. The no-effect-level for elevated fluoride concentrations in bone sections is 20 mg/kg bw/day.

5.1.1 Reliability [redacted]

## Section A6.5 Chronic Toxicity / Carcinogenicity

**Annex Point IIA6.5** 6.5 Chronic toxicity in dogs (2)

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 1, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| | [redacted] |
| | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.6.1 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.1 In-vitro gene mutation study in bacteria (Salmonella typhimurium-reverse mutation assay)

Official use only

### 1 REFERENCE

**1.1 Reference** [redacted] (1994), KUE 13183b - Salmonella/microsome test, [redacted] 1994-01-27 (unpublished)

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** [redacted]

84/449/EEC B.14.; OECD no. 471

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

### 3 MATERIALS AND METHODS

Tolylfluanid ([redacted] was tested for mutagenicity in *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 using the plate incorporation assay. [redacted]

**Section A6.6.1** **Genotoxicity in vitro**

**Annex Point IIA6.6** 6.6.1 In-vitro gene mutation study in bacteria (Salmonella typhimurium-reverse mutation assay)

**4 RESULTS AND DISCUSSION**

[redacted]

**5 CONCLUSION**

**5.1 Conclusion**

[redacted]. Tolylfluanid did not induce any dose-dependent increases in revertant counts in four strains of *S. typhimurium* at subtoxic dose levels with or without S9 mix (three different concentrations of S9). The overall conclusion is that tolylfluanid was not mutagenic in the Ames/Salmonella test.

5.1.1 Reliability [redacted]

## Section A6.6.1 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.1 In-vitro gene mutation study in bacteria (Salmonella typhimurium-reverse mutation assay)

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 16, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.6.2 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.2 In-vitro cytogenicity study in cultured mammalian cells

Official use only

### 1 REFERENCE

| | | |
|---|---|---|
| **1.1** | **Reference** | [redacted] (2004), Chromosomal Aberration Study of Preventol A5-S in Cultured Mammalian Cells. [redacted], date: 2004-08-09 (unpublished) |
| **1.2** | **Data protection** | [redacted] |
| 1.2.1 | Data owner | [redacted] |
| 1.2.2 | Companies with letter of access | – |
| 1.2.3 | Criteria for data protection | [redacted] |

### 2 GUIDELINES AND QUALITY ASSURANCE

| | | |
|---|---|---|
| **2.1** | **Guideline study** | [redacted] Japanese Guideline: Pharmaceutical and Food Affairs No. 1121002. Study design was principally according to OECD Guideline 473. |
| **2.2** | **GLP** | [redacted] |
| **2.3** | **Deviations** | [redacted] |

### 3 MATERIALS AND METHODS

| | | |
|---|---|---|
| **3.1** | **Test material** | [redacted] |
| 3.1.1 | Lot/Batch number | [redacted] |
| 3.1.2 | Specification | [redacted] |
| 3.1.2.1 | Description | [redacted] |
| 3.1.2.2 | Purity | [redacted] |
| 3.1.2.3 | Stability | [redacted] |
| **3.2** | **Study Type** | In vitro mammalian chromosome aberration test |
| 3.2.1 | Organism/cell type | CHL/IU derived from the lungs of female Chinese hamster. |
| 3.2.2 | Deficiencies / Proficiencies | – |
| 3.2.3 | Metabolic activation system | S9 mix<br>S9 fraction was prepared from the livers of 7-week old male Sprague-Dawley rats treated with phenobarbital (PB, 4 times at 24-h intervals, i.p., 30, 60, 60, and 60 mg/kg, respectively) and with 5,6-benzoflavone (single dose, i.p., 80 mg/kg, on the day of the third PB injection). |
| 3.2.4 | Positive control | Without S9 mix: mitomycin C (0.1 µg/mL)<br>With S9 mix: benzo[a]pyrene (20 µg/mL) |

## Section A6.6.2 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.2 In-vitro cytogenicity study in cultured mammalian cells

| | | |
|---|---|---|
| **3.3** | **Application of test substance** | |
| 3.3.1 | Concentrations | [redacted] |
| 3.3.2 | Way of application | [redacted] |
| 3.3.3 | Pre-incubation time | [redacted] |
| 3.3.4 | Other modifications | [redacted] |
| **3.4** | **Examinations** | |
| 3.4.1 | Number of cells evaluated | [redacted] |

**4 RESULTS AND DISCUSSION**

| | | |
|---|---|---|
| **4.1** | **Genotoxicity** | see Table A6_6_2-1 |
| 4.1.1 | Without metabolic activation | Yes, at ≥ 10 µg/mL |
| 4.1.2 | With metabolic activation | Yes, at ≥ 40 µg/mL |
| **4.2** | **Cytotoxicity** | Yes (see Figure A6_6_2-1).<br>–S9: 52% cell growth at 5 µg/mL<br>+S9: 42% cell growth at 30 µg/mL |

**5 APPLICANT'S SUMMARY AND CONCLUSION**

| | | |
|---|---|---|
| **5.1** | **Materials and methods** | [redacted] |
| **5.2** | **Results and discussion** | As a result of the cell growth inhibition test, the estimated $IC_{50}$ values were 5 and 27 µg/mL in the absence and presence of S9 mix, respectively.<br>In the chromosomal aberration test, the incidences of cells with structural chromosomal aberrations were 6.0% and 13.0% at 7.5 and 10 µg/mL, respectively, in the non-activation assay, and were 8.5%, 21.5%, and 52.5% at 30, 40, and 50 µg/mL, respectively, in the activation assay. |

| | |
|---|---|
| **Section A6.6.2** | **Genotoxicity in vitro** |
| **Annex Point IIA6.6** | 6.6.2 In-vitro cytogenicity study in cultured mammalian cells |

| | | |
|---|---|---|
| **5.3** | **Conclusion** | The test material showed the ability to induce chromosomal aberration in cultured Chinese hamster lung fibroblasts. However, these clastogenic effects occurred at concentrations that were clearly cytotoxic.<br>It can be concluded that Tolylfluanid does not have a specific clastogenic potential in this test system. |
| 5.3.1 | Reliability | [redacted] |
| 5.3.2 | Deficiencies | [redacted] |

## Section A6.6.2 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.2 In-vitro cytogenicity study in cultured mammalian cells

| Evaluation by Competent Authorities | |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | October19, 2005 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Figure A6_6_2-1: Cytotoxicity in the treatment with Tolylfluanid**

**Table A6_6_2-1: Results of the chromosomal aberration test**

## Section A6.6.2 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.2 In-vitro cytogenicity study in mammalian cells

Official use only

### 1 REFERENCE

**1.1 Reference** [redacted]. (1984a), KUE 13183b (c.n. Tolylfluanid) - Cytogenetic study with human lymphocyte cultures in vitro to evaluate for harmful effect on chromosomes, [redacted] 1984-08-06, amended: 2000-10-13 (unpublished)

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** No

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

### 3 MATERIALS AND METHODS

The ability of tolylfluanid ([redacted] to induce chromosome aberrations in cultured human lymphocytes was assayed at doses of 0.1, 1 or 10 µg/ml growth medium in the first test round. [redacted]

## 4 RESULTS AND DISCUSSION

[redacted]

## 5 CONCLUSION

**5.1 Conclusion**

Moderate suppression of mitotic indices, indicating cytotoxicity, in cultured human lymphocytes was observed at the highest tested dose of 10 µg/ml, especially without metabolic activation. Significantly increased numbers of metaphases with aberrations were seen at doses starting from and including 1 µg/ml. Another interesting finding was the induction of polyploidy at doses starting from and including 2.5 µg/ml, which would indicate that tolylfluanid interferes with chromosomal segregation at mitosis. The study is acceptable with some reservations pertaining to deficiencies in reporting. The study shows that tolylfluanid causes chromosomal damage in cultured human lymphocytes. Treatment-related deviations from normal chromosome numbers were also observed.

5.1.1 Reliability [redacted]

## Section A6.6.2 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.2 In-vitro cytogenicity study in mammalian cells

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 16, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Table A6_6_4-1 Determination of mitotic index in human lymphocytes treated with tolylfluanid in the first test round**

| Test group | Dose in µg/ml | Evaluated nuclei | Mitoses | |
|---|---|---|---|---|
| | | | Absolute number | % of negative control |
| **Without S9 mix** | | | | |
| Negative control | | | | |
| Tolylfluanid | | | | |
| -"- | | | | |
| -"- | | | | |
| Mitomycin C | | | | |
| **With S9 mix** | | | | |
| Negative control | | | | |
| Tolylfluanid | | | | |
| -"- | | | | |
| -"- | | | | |
| Cyclophosphamide | | | | |

* $p \leq 0.01$ in Chi-Square test

**Table A6_6_4-2 Summary of results from chromosome aberration analysis of human lymphocytes treated with tolylfluanid without metabolic activation in the first test round**

| Dose µg/ml | Meta-phases | Metaphases with aberrations incl. gaps | | Metaphases with aberrations excl. gaps | | Metaphases with exchanges | | Polyploid nuclei in 400 metaphases | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % |
| 0 | 200 | | | | | | | | |
| 0.1 | 200 | | | | | | | | |
| 1.0 | 200 | | | | | | | | |
| 10.0 | 200 | | | | | | | | |
| MMC 0.05 | 199 | | | | | | | | |

$p \leq 0.01$ in Chi-Square test; MMC = Mitomycin C

**Table A6_6_4-3 Summary of results from chromosome aberration analysis of human lymphocytes treated with tolylfluanid with metabolic activation (S9 mix) in the first test round**

| Dose µg/ml | Meta-phases | Metaphases with aberrations incl. gaps | | Metaphases with aberrations excl. gaps | | Metaphases with exchanges | | Polyploid nuclei in 400 metaphases | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % |
| 0 | 199 | | | | | | | | |
| 0.1 | 200 | | | | | | | | |
| 1.0 | 200 | | | | | | | | |
| 10.0 | 200 | | | | | | | | |
| CP 10.0 | 199 | | | | | | | | |

* $p \leq 0.01$ in Chi-Square test; CP = Cyclophosphamide; [1)] polyploid nuclei in 300 metaphases

**Tables A6_6_4-4 Determination of mitotic index in human lymphocytes treated with tolylfluanid in the second test round**

| Test group | Dose in µg/ml | Evaluated nuclei | Mitoses | |
|---|---|---|---|---|
| | | | Absolute number | % of negative control |
| **Without S9 mix** | | | | |
| Negative control | | | | |
| Tolylfluanid | | | | |
| -"- | | | | |
| -"- | | | | |
| Mitomycin C | | | | |
| **With S9 mix** | | | | |
| Negative control | | | | |
| Tolylfluanid | | | | |
| -"- | | | | |
| -"- | | | | |
| Cyclophosphamide | | | | |

* $p \leq 0.01$ in Chi-Square test

**Tables A6_6_4-5 Summary of results from chromosome aberration analysis of human lymphocytes treated with tolylfluanid without metabolic activation in the second test round**

| Dose µg/ml | Meta-phases | Metaphases with aberrations incl. gaps | | Metaphases with aberrations excl. gaps | | Metaphases with exchanges | | Polyploid nuclei in 400 metaphases | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % |
| 0 | 200 | | | | | | | | |
| 2.5 | 200 | | | | | | | | |
| 5.0 | 200 | | | | | | | | |
| 10.0 | Not evaluated/not analysable | | | | | | | | |
| MMC 0.1 | 200 | | | | | | | | |

$p \leq 0.05$ in Chi-Square test; ** $p \leq 0.01$ in Chi-Square test; MMC = Mitomycin C

**Tables A6_6_4-6 Summary of results from chromosome aberration analysis of human lymphocytes treated with tolylfluanid with metabolic activation (S9 mix) in the second test round**

| Dose µg/ml | Meta-phases | Metaphases with aberrations incl. gaps | | Metaphases with aberrations excl. gaps | | Metaphases with exchanges | | Polyploid nuclei in 400 metaphases | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % |
| 0 | 200 | | | | | | | | |
| 2.5 | 200 | | | | | | | | |
| 5.0 | 200 | | | | | | | | |
| 10.0 | 200 | | | | | | | | |
| CP 10.0 | 200 | | | | | | | | |

* $p \leq 0.05$ in Chi-Square test; ** $p \leq 0.01$ in Chi-Square test; CP = Cyclophosphamide; [1)] polyploid nuclei in 300 metaphases

## Section A6.6.3 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.3 In-vitro gene mutation assay in mammalian cells

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted] (1985) Mutagenicity evaluation of KUE 13183B (c.n. Tolylfluanid) in the mouse lymphoma forward mutation assay. [redacted] 1985-02-01 (unpublished)

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** No

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

### 3 MATERIALS AND METHODS

Tolylfluanid ([redacted] was tested for mutagenicity in the mouse lymphoma cell line L5178Y. The test system is designed to detect direct mutations in cells heterozygous at the thymidine kinase ($TK^{+/-}$) locus.

[redacted]

**Section A6.6.3** **Genotoxicity in vitro**

**Annex Point IIA6.6** 6.6.3 In-vitro gene mutation assay in mammalian cells

[redacted]

**4 RESULTS AND DISCUSSION**

[redacted]

**5 CONCLUSION**

**5.1 Conclusion** The test was poorly reported. Tolylfluanid induced mutations in the mouse lymphoma L5178Y (TK +/-) assay with and without metabolic activation.

5.1.1 Reliability [redacted]

## Section A6.6.3 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.3 In-vitro gene mutation assay in mammalian cells

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | December 17, 2005 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Section A6.6.3** **Genotoxicity in vitro**

**Annex Point IIA6.6** 6.6.3 In-vitro gene mutation assay in mammalian cells

Official use only

## 1 REFERENCE

**1.1 Reference**

[redacted] (1987) Mutagenicity test on KUE 13183b in the CHO/HGPRT forward mutation assay. [redacted] 1987-08-24 (unpublished)

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

## 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study**

The study was performed in compliance with OECD guideline 476 (Directive 67/548/EEC, Annex V, Method B.17).

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

## 3 MATERIALS AND METHODS

Tolylfluanid ([redacted] was tested for mutagenicity in the CHO/HGPRT gene mutation assay. Mutants with inactive HGPRT genes were selected for by using the purine analog 6-thioguanine (TG).

[redacted]

[redacted]

## 4 RESULTS AND DISCUSSION

**4.1 Deviations**

[redacted]

## 5 CONCLUSION

**5.1 Conclusion**

[redacted]. Tolylfluanid was not mutagenic in the CHO/HGPRT gene mutation assay with or without metabolic activation, according to the criteria set out in the study protocol, as no repeatable dose-dependent increases in mutation frequencies were observed. The data did, however, show on several occasions statistically significant increases in mutation frequencies, and the absolute levels were in many cases fairly high in comparison to the controls. Overall, the mutagenicity test result may therefore be considered equivocal.

5.1.1 Reliability [redacted]

5.1.2 Deficiencies [redacted]

## Section A6.6.3 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.3 In-vitro gene mutation assay in mammalian cells

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 20, 2008 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | [redacted] |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Section A6.6.3** **Genotoxicity in vitro**

**Annex Point IIA6.6** 6.6.3 In-vitro unscheduled DNA synthesis in mammalian cells

Official use only

## 1 REFERENCE

**1.1 Reference**

[redacted] (1995) KUE 13183B - Test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro. [redacted] 1995-10-31 (unpublished)

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

## 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** [redacted]

OECD guideline 482 (Directive 67/548/EEC, Annex V, Method B.18)

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

## 3 MATERIALS AND METHODS

Tolylfluanid ([redacted] was tested for genotoxicity in the *in vitro* rat primary hepatocyte unscheduled DNA synthesis (UDS) assay.

[redacted]

[redacted]

## 4 RESULTS AND DISCUSSION

[redacted]

## 5 CONCLUSION

**5.1 Conclusion**

[redacted]. Tolylfluanid did not induce DNA repair activity in rat hepatocytes, *in vitro*, at dose levels extending to cytotoxic concentrations.

5.1.1 Reliability [redacted]

## Section A6.6.3 Genotoxicity in vitro

**Annex Point IIA6.6** 6.6.3 In-vitro unscheduled DNA synthesis in mammalian cells

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 20, 200 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.6.4

**Annex Point IIA6.6**

## Genotoxicity in vivo

6.6.4 In-vo mammalian bone marrow cytogenetic test

Official use only

### 1 REFERENCE

**1.1 Reference**

[redacted] (1980) KUE 13183 b (Tolylfluanid) - Micronucleus test on the mouse to evaluate for mutagenic effect. [redacted], 1980-05-13 (unpublished)

[redacted]

**1.2 Data protection**

[redacted]

1.2.1 Data owner

[redacted]

1.2.2 Companies with letter of access

[redacted]

1.2.3 Criteria for data protection

[redacted]

### 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study**

[redacted]

The study was performed according to methods published in the scientific literature.

**2.2 GLP**

[redacted]

**2.3 Deviations**

[redacted]

### 3 MATERIALS AND METHODS

Tolylfluanid ([redacted] was tested for induction of micronuclei in polychromatic erythrocytes of the bone marrow in mice. [redacted]

## 4 RESULTS AND DISCUSSION

[redacted]

## 5 CONCLUSION

### 5.1 Conclusion

[redacted]. No inhibition of bone marrow erythropoiesis was observed with tolylfluanid. Tolylfluanid did not induce micronuclei in polychromatic bone marrow erythrocytes in mouse at doses up to 500 mg/kg, keeping in mind the above mentioned limitations in the test protocol.

5.1.1 Reliability [redacted]

## Section A6.6.4

**Annex Point IIA6.6**

## Genotoxicity in vivo

6.6.4 In-vivo mammalian bone marrow cytogenetic test

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 20, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

**Section A6.6.4** **Genotoxicity in vivo**

**Annex Point IIA6.6** 6.6.4 In-vivo mammalian bone marrow chromosomal analysis

Official use only

## 1 REFERENCE

**1.1 Reference**

[redacted]1990) Chromosome aberration assay in bone marrow cells of the Chinese hamster with KUE 13183b. [redacted], [redacted], 1990-09-20 (unpublished)

[redacted]

**1.2 Data protection** [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

## 2 GUIDELINES AND QUALITY ASSURANCE

**2.1 Guideline study** [redacted]

OECD guideline 475 (Directive 67/548/EEC, Annex V, Method B.11)

**2.2 GLP** [redacted]

**2.3 Deviations** [redacted]

## 3 MATERIALS AND METHODS

Tolylfluanid ([redacted] was tested for induction of chromosome aberrations in bone marrow cells of Chinese hamster. [redacted]

## 4 RESULTS AND DISCUSSION

[redacted]

[redacted]

## 5 CONCLUSION

**5.1 Conclusion**

Very little data is given on possible toxicity related to treatment with tolylfluanid. Three out of ten animals died during the study, but it is not clear if the deaths are related to treatment with the test sample, especially as no data on clinical signs are reported. In the previous bone marrow cytogenetic study in Chinese hamster ([redacted], 1980), no clinical signs or deaths were reported at 4000 mg/kg bw at sacrifice times up to 48 h. Also, as mitotic indices at treatment with 4000 mg/kg bw tolylfluanid were not depressed, it must be concluded that there is conflicting evidence of treatment at toxic conditions in the study described here. Only one sampling time was used (12 h) which does not fulfil the requirements of the official test guidelines. The study is therefore not acceptable as a mutagenicity test and gives only limited evidence of the chromosome damaging potential of tolylfluanid in Chinese hamster *in vivo*.

5.1.1 Reliability [redacted]

## Section A6.6.4

**Annex Point IIA6.6**

## Genotoxicity in vivo

6.6.4 In-vivo mammalian bone marrow chromosomal analysis

| | Evaluation by Competent Authorities |
|---|---|
| | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted |
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | March 20, 2006 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | |
| | **COMMENTS FROM ...** |
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss if deviating from view of rapporteur member state* |
| **Conclusion** | *Discuss if deviating from view of rapporteur member state* |
| **Reliability** | *Discuss if deviating from view of rapporteur member state* |
| **Acceptability** | *Discuss if deviating from view of rapporteur member state* |
| **Remarks** | |

## Section A6.6.4 Genotoxicity in vivo

**Annex Point IIA6.6** 6.6.4 In vivo cytogenetic study of the bone marrow in Chinese hamsters (cytogenetic in-vivo-test)

| | | | Official use only |
|---|---|---|---|
| | | **1 REFERENCE** | |
| **1.1** | **Reference** | [redacted] (2004): KUE 13183B – In Vivo Bone Marrow Cytogenetic Study Using Male Mice. [redacted], 2004-04-08 (unpublished). | |
| **1.2** | **Data protection** | [redacted] | |
| 1.2.1 | Data owner | [redacted] | |
| 1.2.2 | Companies with letter of access | [redacted] | |
| 1.2.3 | Criteria for data protection | [redacted] | |
| | | **2 GUIDELINES AND QUALITY ASSURANCE** | |
| **2.1** | **Guideline study** | [redacted]<br>Directive 2000/32/EC Method B.11;<br>OECD Guideline 475 (July 1997)<br>OPPTS 870.5385 | |
| **2.2** | **GLP** | [redacted] | |
| **2.3** | **Deviations** | [redacted]<br>- [redacted] | |
| | | **3 MATERIALS AND METHODS** | |
| **3.1** | **Test material** | [redacted] | |
| 3.1.1 | Lot/Batch number | [redacted] | |
| 3.1.2 | Specification | [redacted] | |
| 3.1.2.1 | Description | [redacted] | |
| 3.1.2.2 | Purity | [redacted] | |
| 3.1.2.3 | Stability | [redacted] | |
| 3.1.2.4 | Maximum tolerable dose | [redacted] | |
| **3.2** | **Test Animals** | | |
| 3.2.1 | Species | *Mus musculus* | |
| 3.2.2 | Strain | Hsd/Win: NMRI | X |
| 3.2.3 | Source | [redacted] | |
| 3.2.4 | Sex | Males (males and females were used in a pilot study, no sex difference in toxicity was observed) | |
| 3.2.5 | Age/weight at study initiation | [redacted] | |

## Section A6.6.4 Genotoxicity in vivo

**Annex Point IIA6.6** 6.6.4 In vivo cytogenetic study of the bone marrow in Chinese hamsters (cytogenetic in-vivo-test)

| | | |
|---|---|---|
| 3.2.6 | Number of animals per group | [redacted] |
| 3.2.7 | Control animals | [redacted] |
| **3.3** | **Administration/ Exposure** | [redacted] |
| 3.3.1 | Number of applications | [redacted] |
| 3.3.2 | Interval between applications | [redacted] |
| 3.3.3 | Postexposure period | [redacted] |
| 3.3.4 | Type | [redacted] |
| 3.3.5 | Concentration | [redacted] |
| 3.3.6 | Vehicle | [redacted] |
| 3.3.7 | Concentration in vehicle | [redacted] |
| 3.3.8 | Total volume applied | [redacted] |
| 3.3.9 | Controls | [redacted] |
| **3.4** | **Examinations** | |
| 3.4.1 | Clinical signs | [redacted] |
| 3.4.2 | Tissue | [redacted] |
| **3.5** | **Further remarks** | [redacted] |