

Table 1 Mortality - Female rats

| Dose (mg/kg) | Step | Time after administration | | | | | | | | | | Final mortality |
|-----------------|------|---------------------------|-------|---|---|---|---|---|---|---|-----------|--------------------|
| | | 0.5 | 4 hrs | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8-14 days | |
| 2000 | 1st | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 / 3 ^a |
| 2000 | 2nd | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 / 3 |

^a: Cumulative number of animals found dead during the observation period per number of animals treated.

Table 2 Clinical observation - Incidence of signs in female rats

| Clinical sign | Dose (mg/kg) | 2000 | | 2000 | |
|---------------------------|-------------------------|------|----|------|----|
| | Step | 1st | | 2nd | |
| | Fate | fd | tk | fd | tk |
| | No. of animals examined | - | 3 | - | 3 |
| No abnormalities detected | | - | 3 | - | 3 |

Fate: fd, found dead; tk, terminal kill.

Table 3 Body weight - Individual values in female rats

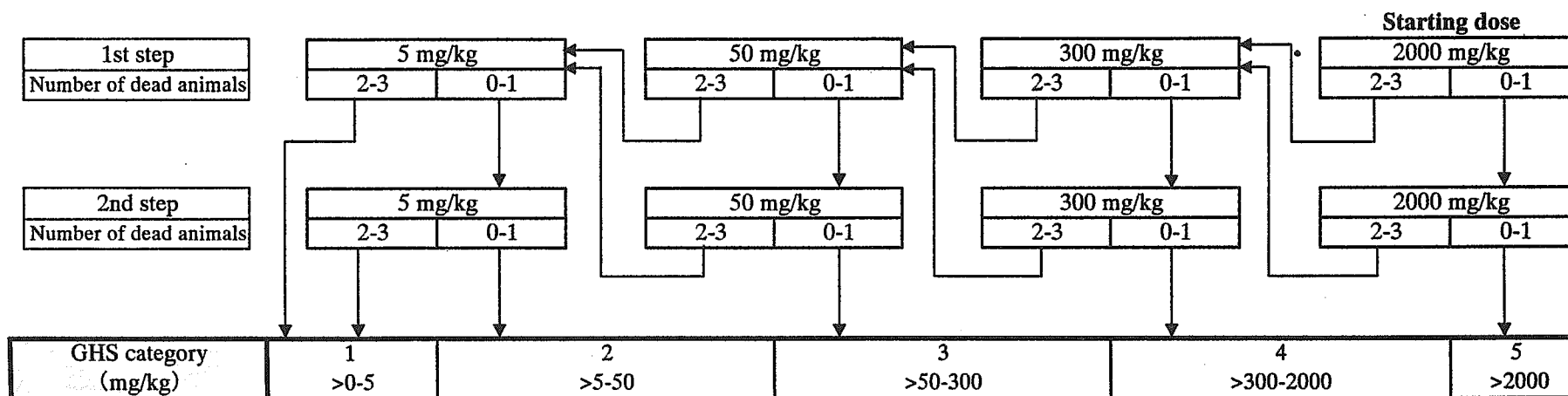
| Dose (mg/kg) | Step | Animal number | Before administration | Days after administration | |
|-----------------|------|------------------|--------------------------|---------------------------|-----|
| | | | | 7 | 14 |
| 2000 | 1st | 111 | 145 | 183 | 193 |
| | | 112 | 154 | 189 | 199 |
| | | 113 | 151 | 180 | 185 |
| 2000 | 2nd | 114 | 148 | 181 | 192 |
| | | 115 | 154 | 185 | 188 |
| | | 116 | 155 | 189 | 201 |

Table 4 Necropsy - Incidence of macroscopic lesions in female rats

| Site and lesion | Dose (mg/kg) | | 2000 | | |
|---------------------------|-------------------------|---|------|-----|---|
| | Step | | 2000 | | |
| | | | 1st | 2nd | |
| | Fate | | fd | tk | |
| | No. of animals examined | - | 3 | - | 3 |
| No abnormalities detected | | - | 3 | - | 3 |

Fate: fd, found dead; tk, terminal kill.

Appendix 1 Flow chart of acute toxic class method with a starting dose of 2000 mg/kg body weight



Appendix 2 Mortality - Identification of scheduled or unscheduled death in female rats

| Dose (mg/kg) | Step | Time after administration | | | | | | | | | | | |
|-----------------|------|---------------------------|-------|---|---|---|---|---|---|---|------|---------|-------|
| | | 0.5 | 4 hrs | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8-13 | 14 days | |
| 2000 | 1st | | | | | | | | | | | (111) | (112) |
| | | | | | | | | | | | | | (113) |
| 2000 | 2nd | | | | | | | | | | | (114) | (115) |
| | | | | | | | | | | | | | (116) |

(n): Scheduled death.

Appendix 3 Clinical observation - Individual data in female rats

| Dose (mg/kg) | Step | Animal number | Fate | Time of death | Clinical signs |
|--------------|------|---------------|------|---------------|---------------------------|
| 2000 | 1st | 111 | tk | 14d | No abnormalities detected |
| | | 112 | tk | 14d | No abnormalities detected |
| | | 113 | tk | 14d | No abnormalities detected |
| 2000 | 2nd | 114 | tk | 14d | No abnormalities detected |
| | | 115 | tk | 14d | No abnormalities detected |
| | | 116 | tk | 14d | No abnormalities detected |

Fate: tk, terminal kill.

Time: d, days.

Appendix 4 Necropsy - Individual macroscopic lesions in female rats

| Dose (mg/kg) | Step | Animal number | Fate | Time of death | Macroscopic lesions |
|--------------|------|---------------|------|---------------|---------------------------|
| 2000 | 1st | 111 | tk | 14d | No abnormalities detected |
| | | 112 | tk | 14d | No abnormalities detected |
| | | 113 | tk | 14d | No abnormalities detected |
| 2000 | 2nd | 114 | tk | 14d | No abnormalities detected |
| | | 115 | tk | 14d | No abnormalities detected |
| | | 116 | tk | 14d | No abnormalities detected |

Fate: tk, terminal kill.

Time: d, days.

Appendix 5

Environmental control - Temperature in the animal room
(Animal Room 116)

(°C)

| Day | Month Year | November 2003 | December 2003 |
|-----|---------------|------------------|------------------|
| 1 | | - | 21.5 ~ 22.1 |
| 2 | | - | 21.8 ~ 22.0 |
| 3 | | - | 21.9 ~ 22.0 |
| 4 | | - | 21.8 ~ 22.0 |
| 5 | | - | 21.9 ~ 22.0 |
| 6 | | - | 21.9 ~ 21.9 |
| 7 | | - | 21.6 ~ 22.0 |
| 8 | | - | 21.8 ~ 22.0 |
| 9 | | - | 21.8 ~ 22.0 |
| 10 | | - | 21.8 ~ 22.2 |
| 11 | | - | 21.8 ~ 21.9 |
| 12 | | - | 21.8 ~ 22.0 |
| 13 | | - | 21.8 ~ 22.0 |
| 14 | | - | 21.8 ~ 22.2 |
| 15 | | - | 21.8 ~ 22.2 |
| 16 | | - | 21.8 ~ 22.0 |
| 17 | | - | - |
| 18 | | 21.8 ~ 22.0 | - |
| 19 | | 21.8 ~ 22.0 | - |
| 20 | | 21.8 ~ 22.0 | - |
| 21 | | 21.9 ~ 22.0 | - |
| 22 | | 21.9 ~ 22.2 | - |
| 23 | | 21.9 ~ 22.1 | - |
| 24 | | 21.8 ~ 22.0 | - |
| 25 | | 21.8 ~ 21.9 | - |
| 26 | | 21.8 ~ 22.0 | - |
| 27 | | 21.8 ~ 22.0 | - |
| 28 | | 21.8 ~ 22.0 | - |
| 29 | | 21.9 ~ 22.0 | - |
| 30 | | 21.8 ~ 22.0 | - |
| 31 | | - | - |

-: Data not shown because of the absence of animals in the room.

Appendix 6 Environmental control - Humidity in the animal room
(Animal Room 116)

| | | (%) | |
|-----|---------------|------------------|--------------------------|
| Day | Month Year | November 2003 | December 2003 |
| 1 | | - | 47.8 ~ 59.1 |
| 2 | | - | 52.8 ~ 71.3 ^a |
| 3 | | - | 51.7 ~ 55.1 |
| 4 | | - | 52.2 ~ 55.9 |
| 5 | | - | 52.7 ~ 58.3 |
| 6 | | - | 55.3 ~ 59.4 |
| 7 | | - | 53.1 ~ 60.8 |
| 8 | | - | 53.0 ~ 61.1 |
| 9 | | - | 53.0 ~ 64.5 |
| 10 | | - | 52.6 ~ 61.5 |
| 11 | | - | 50.8 ~ 57.6 |
| 12 | | - | 55.4 ~ 60.2 |
| 13 | | - | 54.7 ~ 64.8 |
| 14 | | - | 53.5 ~ 61.4 |
| 15 | | - | 52.9 ~ 62.7 |
| 16 | | - | 53.2 ~ 64.4 |
| 17 | | - | - |
| 18 | | 50.1 ~ 54.2 | - |
| 19 | | 50.3 ~ 52.5 | - |
| 20 | | 49.8 ~ 51.6 | - |
| 21 | | 47.6 ~ 54.0 | - |
| 22 | | 47.2 ~ 58.7 | - |
| 23 | | 49.5 ~ 54.9 | - |
| 24 | | 49.9 ~ 53.5 | - |
| 25 | | 49.4 ~ 56.1 | - |
| 26 | | 49.0 ~ 55.2 | - |
| 27 | | 53.0 ~ 56.4 | - |
| 28 | | 53.3 ~ 59.8 | - |
| 29 | | 53.2 ~ 57.1 | - |
| 30 | | 48.2 ~ 58.2 | - |
| 31 | | - | - |

-: Data not shown because of the absence of animals in the room.

a: A temporal rise following cleaning of the animal room (≤ 1.8 h).