

Table 4 General signs of dams during lactation in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group       | mg/kg | Number of dams<br>and general signs | Days of lactation |      |     |      |     |      |     |      |     |      |     |      |     |      |    |    |
|-------------|-------|-------------------------------------|-------------------|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|----|----|
|             |       |                                     | 0                 |      | 1   |      | 2   |      | 3   |      | 4   |      | 5   |      | 6   |      | 7  |    |
|             |       |                                     | Pre               | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |    |    |
| Control     | 0     | Number of dams                      | 11                | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11 |    |
|             |       | Normal                              | 11                | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11 | 11 |
| bumetrizole | 62.5  | Number of dams                      | 12                | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12 |    |
|             |       | Normal                              | 12                | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12 | 12 |
|             | 250   | Number of dams                      | 12                | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12 | 12 |
|             |       | Normal                              | 12                | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12  | 12   | 12 | 12 |
|             | 1000  | Number of dams                      | 11                | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11 | 11 |
|             |       | Normal                              | 11                | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11  | 11   | 11 | 11 |

Pre: Before administration, Post: after administration.

Table 5-1 General signs of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group       | mg/kg | Number of females and general signs | Days of administration |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |  |  |
|-------------|-------|-------------------------------------|------------------------|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|--|--|
|             |       |                                     | 1                      |      | 2   |      | 3   |      | 4   |      | 5   |      | 6   |      | 7   |      | 8   |      | 9   |      | 10  |      | 11  |      | 12  |      | 13  |      |  |  |
|             |       |                                     | Pre                    | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |  |  |
| Control     | 0     | Number of females                   | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    |  |  |
|             |       | Normal                              | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    |  |  |
| bumetrizole | 250   | Number of females                   | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    |  |  |
|             |       | Normal                              | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    |  |  |
|             | 1000  | Number of females                   | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    |  |  |
|             |       | Normal                              | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    |  |  |

Pre: Before administration, Post: after administration.

Table 5-2 General signs of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group       | mg/kg | Number of females and general signs | Days of administration |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |
|-------------|-------|-------------------------------------|------------------------|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|
|             |       |                                     | 14                     |      | 15  |      | 16  |      | 17  |      | 18  |      | 19  |      | 20  |      | 21  |      | 22  |      | 23  |      | 24  |      | 25  |      | 26  |      |
|             |       |                                     | Pre                    | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Control     | 0     | Number of females                   | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
|             |       | Normal                              | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
| bumetrizole | 250   | Number of females                   | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
|             |       | Normal                              | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
|             | 1000  | Number of females                   | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
|             |       | Normal                              | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |

Pre: Before administration, Post: after administration.

Table 5-3 General signs of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group       | mg/kg | Number of females and general signs | Days of administration |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |     |      |
|-------------|-------|-------------------------------------|------------------------|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|
|             |       |                                     | 27                     |      | 28  |      | 29  |      | 30  |      | 31  |      | 32  |      | 33  |      | 34  |      | 35  |      | 36  |      | 37  |      | 38  |      | 39  |      |
|             |       |                                     | Pre                    | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Control     | 0     | Number of females                   | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
|             |       | Normal                              | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
| bumetrizole | 250   | Number of females                   | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
|             |       | Normal                              | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
|             | 1000  | Number of females                   | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |
|             |       | Normal                              | 6                      | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6   |      |

Pre: Before administration, Post: after administration.

Table 5-4 General signs of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group       | mg/kg | Number of females<br>and general signs | Days of administration |      |     |      |     |      |
|-------------|-------|--|------------------------|------|-----|------|-----|------|
|             |       |  | 40                     |      | 41  |      | 42  |      |
|             |       |  | Pre                    | Post | Pre | Post | Pre | Post |
| Control     | 0     | Number of females                      | 6                      | 6    | 6   | 6    | 6   | 6    |
|             |       | Normal                                 | 6                      | 6    | 6   | 6    | 6   | 6    |
| bumetrizole | 250   | Number of females                      | 6                      | 6    | 6   | 6    | 6   | 6    |
|             |       | Normal                                 | 6                      | 6    | 6   | 6    | 6   | 6    |
|             | 1000  | Number of females                      | 6                      | 6    | 6   | 6    | 6   | 6    |
|             |       | Normal                                 | 6                      | 6    | 6   | 6    | 6   | 6    |

Pre: Before administration, Post: after administration.

Table 5-5 General signs of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group       | mg/kg | Number of females<br>and general signs | Days of recovery |   |   |   |   |   |   |   |   |    |    |    |    |    |    |   |
|-------------|-------|--|------------------|---|---|---|---|---|---|---|---|----|----|----|----|----|----|---|
|             |       |  | 1                | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |   |
| Control     | 0     | Number of females                      | 6                | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6  | 6  | 6  | 6  | 6  | 6  |   |
|             |       | Normal                                 | 6                | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6  | 6  | 6  | 6  | 6  | 6  | 6 |
| bumetrizole | 250   | Number of females                      | 6                | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6  | 6  | 6  | 6  | 6  | 6  |   |
|             |       | Normal                                 | 6                | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6  | 6  | 6  | 6  | 6  | 6  | 6 |
|             | 1000  | Number of females                      | 6                | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6  | 6  | 6  | 6  | 6  | 6  | 6 |
|             |       | Normal                                 | 6                | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6  | 6  | 6  | 6  | 6  | 6  | 6 |

Table 6 Body weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                  | Control  | bumetrizole |          |          |
|------------------------|----------|-------------|----------|----------|
| mg/kg                  | 0        | 62.5        | 250      | 1000     |
| Number of males        | 12       | 12          | 12       | 12       |
| Days of administration |          |             |          |          |
| 1                      | 381 ± 12 | 380 ± 11    | 381 ± 12 | 380 ± 13 |
| 4                      | 395 ± 14 | 392 ± 12    | 389 ± 13 | 389 ± 12 |
| 8                      | 409 ± 20 | 404 ± 14    | 401 ± 14 | 404 ± 13 |
| 11                     | 419 ± 20 | 415 ± 18    | 410 ± 15 | 415 ± 15 |
| 15                     | 429 ± 22 | 425 ± 17    | 420 ± 18 | 422 ± 16 |
| 18                     | 434 ± 23 | 434 ± 22    | 427 ± 19 | 429 ± 18 |
| 22                     | 446 ± 23 | 446 ± 22    | 442 ± 20 | 442 ± 18 |
| 25                     | 456 ± 25 | 457 ± 23    | 452 ± 23 | 454 ± 21 |
| 29                     | 469 ± 26 | 468 ± 24    | 465 ± 23 | 463 ± 24 |
| 32                     | 477 ± 28 | 477 ± 23    | 473 ± 23 | 472 ± 24 |
| 36                     | 488 ± 30 | 488 ± 24    | 484 ± 26 | 481 ± 24 |
| 39                     | 495 ± 31 | 493 ± 25    | 489 ± 26 | 490 ± 24 |
| 42                     | 496 ± 32 | 497 ± 26    | 487 ± 26 | 490 ± 22 |
| Number of males        | 6        | 6           | 6        | 6        |
| Days of recovery       |          |             |          |          |
| 1                      | 507 ± 30 | 504 ± 26    | 494 ± 35 | 493 ± 30 |
| 4                      | 514 ± 32 | 512 ± 30    | 499 ± 36 | 499 ± 28 |
| 8                      | 523 ± 30 | 522 ± 27    | 508 ± 38 | 507 ± 30 |
| 11                     | 526 ± 31 | 529 ± 28    | 513 ± 39 | 509 ± 32 |
| 14                     | 535 ± 31 | 540 ± 29    | 521 ± 38 | 519 ± 32 |

Each value shows mean (g) ± S.D.

Table 7 Body weights of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                  | Control      |  | bumetrizole |              |              |  |
|------------------------|--------------|--|-------------|--------------|--------------|--|
| mg/kg                  | 0            |  | 62.5        | 250          | 1000         |  |
| Number of females      | 12           |  | 12          | 12           | 12           |  |
| Days of administration |              |  |             |              |              |  |
| 1                      | 250 ± 7      |  | 250 ± 7     | 251 ± 6      | 249 ± 8      |  |
| 4                      | 259 ± 13     |  | 256 ± 9     | 257 ± 6      | 256 ± 10     |  |
| 8                      | 269 ± 15     |  | 266 ± 10    | 266 ± 7      | 264 ± 9      |  |
| 11                     | 272 ± 19     |  | 269 ± 8     | 266 ± 9      | 265 ± 10     |  |
| 15                     | 281 ± 21     |  | 277 ± 9     | 273 ± 10     | 272 ± 11     |  |
| 18                     | 280 ± 10 (6) |  | 307 (1)     | 284 ± 12 (4) | 279 ± 13 (4) |  |
| 22                     | -            |  | -           | -            | 323 (1)      |  |
| 25                     | -            |  | -           | -            | 335 (1)      |  |

Each value shows mean (g) ± S.D.



Table 8 Body weights of dams during pregnancy in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group             | Control  | bumetrizole |          |          |
|-------------------|----------|-------------|----------|----------|
| mg/kg             | 0        | 62.5        | 250      | 1000     |
| Number of dams    | 11       | 12          | 12       | 11       |
| Days of pregnancy |          |             |          |          |
| 0                 | 285 ± 18 | 278 ± 13    | 278 ± 13 | 278 ± 20 |
| 7                 | 324 ± 18 | 319 ± 16    | 316 ± 20 | 316 ± 20 |
| 14                | 359 ± 21 | 354 ± 19    | 351 ± 29 | 351 ± 24 |
| 21                | 444 ± 27 | 444 ± 27    | 443 ± 37 | 443 ± 33 |

Each value shows mean (g) ± S.D.

Table 9 Body weights of dams during lactation in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group             | Control  | bumetrizole |          |          |
|-------------------|----------|-------------|----------|----------|
| mg/kg             | 0        | 62.5        | 250      | 1000     |
| Number of dams    | 11       | 12          | 12       | 11       |
| Days of lactation |          |             |          |          |
| 0                 | 334 ± 25 | 325 ± 24    | 330 ± 35 | 322 ± 29 |
| 4                 | 351 ± 27 | 347 ± 19    | 343 ± 26 | 349 ± 30 |
| 6                 | 335 ± 19 | 332 ± 22    | 334 ± 31 | 327 ± 31 |

Each value shows mean (g) ± S.D.

Table 10 Body weights of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                  | Control  | bumetrizole |          |
|------------------------|----------|-------------|----------|
| mg/kg                  | 0        | 250         | 1000     |
| Number of females      | 6        | 6           | 6        |
| Days of administration |          |             |          |
| 1                      | 257 ± 7  | 258 ± 6     | 257 ± 7  |
| 4                      | 259 ± 13 | 267 ± 11    | 263 ± 11 |
| 8                      | 268 ± 11 | 277 ± 15    | 273 ± 17 |
| 11                     | 270 ± 10 | 279 ± 17    | 276 ± 15 |
| 15                     | 278 ± 12 | 288 ± 17    | 279 ± 16 |
| 18                     | 286 ± 13 | 298 ± 17    | 285 ± 13 |
| 22                     | 293 ± 15 | 305 ± 22    | 293 ± 12 |
| 25                     | 299 ± 16 | 311 ± 20    | 296 ± 11 |
| 29                     | 307 ± 19 | 316 ± 22    | 303 ± 12 |
| 32                     | 304 ± 17 | 317 ± 25    | 301 ± 9  |
| 36                     | 310 ± 20 | 324 ± 24    | 304 ± 9  |
| 39                     | 319 ± 19 | 325 ± 25    | 310 ± 14 |
| 42                     | 322 ± 20 | 328 ± 27    | 315 ± 15 |
| Number of females      | 6        | 6           | 6        |
| Days of recovery       |          |             |          |
| 1                      | 319 ± 22 | 327 ± 25    | 309 ± 13 |
| 4                      | 326 ± 24 | 333 ± 26    | 319 ± 13 |
| 8                      | 333 ± 25 | 338 ± 25    | 321 ± 12 |
| 11                     | 334 ± 23 | 344 ± 21    | 322 ± 9  |
| 14                     | 337 ± 27 | 348 ± 22    | 325 ± 8  |

Each value shows mean (g) ± S.D.

Table 11 Food consumption of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                  | Control | bumetrizole |          |        |
|------------------------|---------|-------------|----------|--------|
| mg/kg                  | 0       | 62.5        | 250      | 1000   |
| Number of males        | 12      | 12          | 12       | 12     |
| Days of administration |         |             |          |        |
| 2                      | 25 ± 3  | 26 ± 3      | 24 ± 3   | 26 ± 3 |
| 5                      | 25 ± 3  | 25 ± 2      | 25 ± 2   | 25 ± 3 |
| 9                      | 24 ± 2  | 25 ± 2      | 24 ± 2   | 25 ± 3 |
| 12                     | 25 ± 2  | 26 ± 2      | 25 ± 3   | 26 ± 4 |
| 30                     | 26 ± 2  | 26 ± 2      | 25 ± 3   | 26 ± 3 |
| 33                     | 25 ± 2  | 26 ± 3      | 26 ± 3   | 25 ± 2 |
| 37                     | 26 ± 2  | 26 ± 2      | 26 ± 2   | 27 ± 2 |
| 40                     | 25 ± 2  | 26 ± 3      | 24 ± 2   | 26 ± 2 |
| Number of males        | 6       | 6           | 6        | 6      |
| Days of recovery       |         |             |          |        |
| 2                      | 24 ± 2  | 24 ± 2      | 23 ± 2   | 23 ± 2 |
| 5                      | 24 ± 2  | 23 ± 1      | 22 ± 1 * | 22 ± 1 |
| 9                      | 26 ± 3  | 26 ± 2      | 26 ± 3   | 25 ± 2 |
| 12                     | 27 ± 3  | 27 ± 1      | 27 ± 2   | 27 ± 3 |

Each value shows mean (g/day) ± S.D.

Significantly different from control group (\*: P<0.05).

Table 12 Food consumption of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                  | Control | bumetrizole |        |        |
|------------------------|---------|-------------|--------|--------|
| mg/kg                  | 0       | 62.5        | 250    | 1000   |
| Number of females      | 12      | 12          | 12     | 12     |
| Days of administration |         |             |        |        |
| 2                      | 19 ± 2  | 19 ± 3      | 18 ± 4 | 19 ± 2 |
| 5                      | 20 ± 2  | 20 ± 3      | 20 ± 3 | 19 ± 4 |
| 9                      | 19 ± 3  | 19 ± 3      | 18 ± 3 | 18 ± 4 |
| 12                     | 20 ± 3  | 19 ± 3      | 19 ± 3 | 18 ± 3 |

Each value shows mean (g/day) ± S.D.

Table 13 Food consumption of dams during pregnancy in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group             | Control | bumetrizole |         |        |
|-------------------|---------|-------------|---------|--------|
| mg/kg             | 0       | 62.5        | 250     | 1000   |
| Number of dams    | 11      | 12          | 12      | 11     |
| Days of pregnancy |         |             |         |        |
| 2                 | 22 ± 3  | 22 ± 2      | 21 ± 3  | 22 ± 2 |
| 9                 | 23 ± 3  | 25 ± 4      | 30 ± 22 | 24 ± 3 |
| 16                | 24 ± 3  | 25 ± 4      | 25 ± 4  | 24 ± 3 |
| 20                | 22 ± 3  | 23 ± 3      | 22 ± 3  | 23 ± 4 |

Each value shows mean (g/day) ± S.D.

Table 14 Food consumption of dams during lactation in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group             | Control | bumetrizole |        |        |        |
|-------------------|---------|-------------|--------|--------|--------|
| mg/kg             | 0       | 62.5        | 250    | 1000   |        |
| Number of dams    | 11      | 12          | 12     | 11     |        |
| Days of lactation | 2       | 30 ± 6      | 30 ± 3 | 27 ± 5 | 33 ± 5 |

Each value shows mean (g/day) ± S.D.

Table 15 Food consumption of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                  | Control | bumetrizole |        |
|------------------------|---------|-------------|--------|
| mg/kg                  | 0       | 250         | 1000   |
| Number of females      | 6       | 6           | 6      |
| Days of administration |         |             |        |
| 2                      | 18 ± 3  | 19 ± 3      | 17 ± 3 |
| 5                      | 19 ± 1  | 18 ± 3      | 20 ± 4 |
| 9                      | 18 ± 2  | 17 ± 4      | 19 ± 3 |
| 12                     | 17 ± 3  | 20 ± 3      | 16 ± 3 |
| 16                     | 17 ± 3  | 19 ± 3      | 14 ± 3 |
| 19                     | 20 ± 3  | 20 ± 4      | 17 ± 3 |
| 23                     | 18 ± 2  | 18 ± 4      | 17 ± 2 |
| 26                     | 20 ± 3  | 21 ± 4      | 19 ± 3 |
| 30                     | 18 ± 4  | 18 ± 4      | 18 ± 2 |
| 33                     | 21 ± 1  | 22 ± 2      | 23 ± 3 |
| 37                     | 18 ± 2  | 17 ± 1      | 18 ± 2 |
| 40                     | 18 ± 3  | 20 ± 3      | 18 ± 3 |
| Number of females      | 6       | 6           | 6      |
| Days of recovery       |         |             |        |
| 2                      | 20 ± 3  | 21 ± 3      | 18 ± 2 |
| 5                      | 22 ± 4  | 19 ± 4      | 20 ± 2 |
| 9                      | 21 ± 4  | 20 ± 4      | 19 ± 3 |
| 12                     | 23 ± 6  | 19 ± 4      | 20 ± 4 |

Each value shows mean (g/day) ± S.D.



Table 16-1 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                           |              | Control |         | bumetrizole |         |
|---------------------------------|--------------|---------|---------|-------------|---------|
| mg/kg                           |              | 0       | 62.5    | 250         | 1000    |
| Number of males                 |              | 12      | 12      | 12          | 12      |
| Observation of animals in cages |              |         |         |             |         |
| Posture                         | Pre          | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                                 | Mean (range) |         |         |             |         |
| Mean (range)                    | Day 7        | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                                 | Day 14       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                                 | Day 21       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                                 | Day 28       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                                 | Day 35       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                                 | Day 41       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                                 | Day 41       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
| Palpebral closure               | Pre          | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Mean (range) |         |         |             |         |
| Mean (range)                    | Day 7        | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 14       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 21       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 28       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 35       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
| Biting behavior                 | Pre          | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Mean (range) |         |         |             |         |
| Mean (range)                    | Day 7        | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 14       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 21       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 28       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 35       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
| Clonic convulsions              | Pre          | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Mean (range) |         |         |             |         |
| Mean (range)                    | Day 7        | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 14       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 21       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 28       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 35       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                                 | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |

Findings were graded as follows

- Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.  
Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.  
Biting behavior 1: Not observed, 2: observed.  
Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Table 16-2 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                           | Control | bumetrizole |         |         |
|---------------------------------|---------|-------------|---------|---------|
| mg/kg                           | 0       | 62.5        | 250     | 1000    |
| Number of males                 | 12      | 12          | 12      | 12      |
| Observation of animals in cages |         |             |         |         |
| Tonic convulsions               |         |             |         |         |
| Pre                             | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Mean (range)                    |         |             |         |         |
| Day 7                           | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Day 14                          | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Day 21                          | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Day 28                          | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Day 35                          | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Day 41                          | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |

Findings were graded as follows

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions, 5: asphyxial convulsions.

Table 16-3 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                                     |              | Control | bumetrizole |         |         |
|---|--------------|---------|-------------|---------|---------|
| mg/kg                                     |              | 0       | 62.5        | 250     | 1000    |
| Number of males                           |              | 12      | 12          | 12      | 12      |
| Observation of animals on observer's palm |              |         |             |         |         |
| Ease of removal from cage                 | Pre          | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Mean (range) |         |             |         |         |
| Mean (range)                              | Day 7        | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 14       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 21       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 28       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 35       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 41       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 41       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
| Ease of handling                          | Pre          | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Mean (range) |         |             |         |         |
| Mean (range)                              | Day 7        | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 14       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 21       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 28       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 35       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 41       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 41       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
| Muscle tone                               | Pre          | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Mean (range) |         |             |         |         |
| Mean (range)                              | Day 7        | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 14       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 21       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 28       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 35       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 41       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
|   | Day 41       | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |
| Fur conditions                            | Pre          | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Mean (range) |         |             |         |         |
| Mean (range)                              | Day 7        | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 14       | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 21       | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 28       | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 35       | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 41       | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 41       | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |

Findings were graded as follows

Ease of removal from cage

1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling

1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing, 3: struggling and trying to bite observer's hand.

Muscle tone

1: Decreased, 2: normal, 3: increased.

Fur conditions

1: Normal, 2: slightly soiled, 3: markedly soiled.

Table 16-4 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                                     |        | Control | bumetrizole |         |         |
|---|--------|---------|-------------|---------|---------|
| mg/kg                                     |        | 0       | 62.5        | 250     | 1000    |
| Number of males                           |        | 12      | 12          | 12      | 12      |
| Observation of animals on observer's palm |        |         |             |         |         |
| Lacrimation                               | Pre    | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Mean (range)                              | Day 7  | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 14 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 21 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 28 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 35 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 41 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Salivation                                | Pre    | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Mean (range)                              | Day 7  | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 14 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 21 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 28 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 35 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 41 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Respiration                               | Pre    | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
| Mean (range)                              | Day 7  | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 14 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 21 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 28 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 35 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |
|   | Day 41 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |

Findings were graded as follows

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

Respiration 1: Normal, 2: bradypnea, 3: dyspnea.

Table 16-5 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                 |              | Control |     | bumetrizole |     |       |     |       |     |
|-----------------------|--------------|---------|-----|-------------|-----|-------|-----|-------|-----|
| mg/kg                 |              | 0       |     | 62.5        |     | 250   |     | 1000  |     |
| Number of males       |              | 12      |     | 12          |     | 12    |     | 12    |     |
| Open-field test       |              |         |     |             |     |       |     |       |     |
| Frequency of rearing  | Pre          | 8.8 ±   | 4.5 | 7.0 ±       | 4.0 | 7.3 ± | 5.1 | 4.9 ± | 4.1 |
|                       | Mean ± S.D.  |         |     |             |     |       |     |       |     |
| Mean ± S.D.           | Day 7        | 3.3 ±   | 3.0 | 1.8 ±       | 2.1 | 2.7 ± | 3.1 | 3.7 ± | 4.9 |
|                       | Day 14       | 2.0 ±   | 2.3 | 2.9 ±       | 3.3 | 1.0 ± | 1.7 | 3.8 ± | 3.7 |
|                       | Day 21       | 2.3 ±   | 2.5 | 2.5 ±       | 2.5 | 2.1 ± | 3.2 | 2.4 ± | 2.5 |
|                       | Day 28       | 3.3 ±   | 2.9 | 3.3 ±       | 4.9 | 4.1 ± | 4.3 | 3.3 ± | 2.6 |
|                       | Day 35       | 3.4 ±   | 3.5 | 2.8 ±       | 3.1 | 3.2 ± | 2.7 | 2.5 ± | 2.5 |
|                       | Day 41       | 5.1 ±   | 4.3 | 2.7 ±       | 3.7 | 4.0 ± | 3.5 | 5.0 ± | 3.7 |
|                       | Day 41       | 5.1 ±   | 4.3 | 2.7 ±       | 3.7 | 4.0 ± | 3.5 | 5.0 ± | 3.7 |
| Frequency of grooming | Pre          | 0.0 ±   | 0.0 | 0.0 ±       | 0.0 | 0.0 ± | 0.0 | 0.0 ± | 0.0 |
|                       | Mean ± S.D.  |         |     |             |     |       |     |       |     |
| Mean ± S.D.           | Day 7        | 0.0 ±   | 0.0 | 0.0 ±       | 0.0 | 0.0 ± | 0.0 | 0.0 ± | 0.0 |
|                       | Day 14       | 0.1 ±   | 0.3 | 0.0 ±       | 0.0 | 0.0 ± | 0.0 | 0.0 ± | 0.0 |
|                       | Day 21       | 0.0 ±   | 0.0 | 0.0 ±       | 0.0 | 0.0 ± | 0.0 | 0.0 ± | 0.0 |
|                       | Day 28       | 0.0 ±   | 0.0 | 0.0 ±       | 0.0 | 0.0 ± | 0.0 | 0.0 ± | 0.0 |
|                       | Day 35       | 0.0 ±   | 0.0 | 0.0 ±       | 0.0 | 0.0 ± | 0.0 | 0.0 ± | 0.0 |
|                       | Day 41       | 0.0 ±   | 0.0 | 0.0 ±       | 0.0 | 0.0 ± | 0.0 | 0.0 ± | 0.0 |
|                       | Day 41       | 0.0 ±   | 0.0 | 0.0 ±       | 0.0 | 0.0 ± | 0.0 | 0.0 ± | 0.0 |
| Gait                  | Pre          | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Mean (range) |         |     |             |     |       |     |       |     |
| Mean (range)          | Day 7        | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 14       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 21       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 28       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 35       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 41       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 41       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
| Palpebral closure     | Pre          | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Mean (range) |         |     |             |     |       |     |       |     |
| Mean (range)          | Day 7        | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 14       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 21       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 28       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 35       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 41       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |
|                       | Day 41       | 1.0     | (1) | 1.0         | (1) | 1.0   | (1) | 1.0   | (1) |

Frequency of rearing (during a 2-minute period).

Frequency of grooming (during a 2-minute period).

Findings were graded as follows

Gait

1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged, unable to support body, 7: standing on tiptoe.

Palpebral closure

1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Table 16-6 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                    |              | Control |         | bumetrizole |         |
|--------------------------|--------------|---------|---------|-------------|---------|
| mg/kg                    |              | 0       | 62.5    | 250         | 1000    |
| Number of males          |              | 12      | 12      | 12          | 12      |
| Open-field test          |              |         |         |             |         |
| Consciousness            | Pre          | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                          | Mean (range) |         |         |             |         |
| Mean (range)             | Day 7        | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                          | Day 14       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                          | Day 21       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                          | Day 28       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                          | Day 35       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                          | Day 41       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
|                          | Day 41       | 2.0 (2) | 2.0 (2) | 2.0 (2)     | 2.0 (2) |
| Behavioral abnormalities | Pre          | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Mean (range) |         |         |             |         |
| Mean (range)             | Day 7        | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 14       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 21       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 28       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 35       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
| Righting reflex          | Pre          | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Mean (range) |         |         |             |         |
| Mean (range)             | Day 7        | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 14       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 21       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 28       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 35       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |
|                          | Day 41       | 1.0 (1) | 1.0 (1) | 1.0 (1)     | 1.0 (1) |

Findings were graded as follows

Consciousness

1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities

1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Table 17-1 FOB of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                           | Control             |              | bumetrizole |         |         |      |
|---------------------------------|---------------------|--------------|-------------|---------|---------|------|
| mg/kg                           | 0                   |              | 62.5        | 250     | 1000    |      |
| Number of females               | 12                  |              | 12          | 12      | 12      |      |
| Observation of animals in cages |                     |              |             |         |         |      |
| Posture                         | Pre                 | 2.0 (2)      | 2.0 (2)     | 2.0 (2) | 2.0 (2) |      |
| Mean (range)                    | Day 8               | 2.0 (2)      | 2.0 (2)     | 2.0 (2) | 2.0 (2) |      |
|                                 | Day 15              | 2.0 (2)      | 2.0 (2)     | 2.0 (2) | 2.0 (2) |      |
|                                 | Day 1 of pregnancy  | 2.0 (2) [11] | 2.0 (2)     | 2.0 (2) | 2.0 (2) | [11] |
|                                 | Day 8 of pregnancy  | 2.0 (2) [11] | 2.0 (2)     | 2.0 (2) | 2.0 (2) | [11] |
|                                 | Day 15 of pregnancy | 2.0 (2) [11] | 2.0 (2)     | 2.0 (2) | 2.0 (2) | [11] |
|                                 | Day 3 of lactation  | 2.0 (2) [11] | 2.0 (2)     | 2.0 (2) | 2.0 (2) | [11] |
| Palpebral closure               | Pre                 | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
| Mean (range)                    | Day 8               | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
|                                 | Day 15              | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
|                                 | Day 1 of pregnancy  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 8 of pregnancy  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 15 of pregnancy | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 3 of lactation  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
| Biting behavior                 | Pre                 | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
| Mean (range)                    | Day 8               | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
|                                 | Day 15              | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
|                                 | Day 1 of pregnancy  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 8 of pregnancy  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 15 of pregnancy | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 3 of lactation  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
| Clonic convulsions              | Pre                 | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
| Mean (range)                    | Day 8               | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
|                                 | Day 15              | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
|                                 | Day 1 of pregnancy  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 8 of pregnancy  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 15 of pregnancy | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 3 of lactation  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |

Figures in parentheses [ ] indicate number of females.

Findings were graded as follows

- Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.  
Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.  
Biting behavior 1: Not observed, 2: observed.  
Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Table 17-2 FOB of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                           | Control             |              | bumetrizole |         |         |      |
|---------------------------------|---------------------|--------------|-------------|---------|---------|------|
| mg/kg                           | 0                   |              | 62.5        | 250     | 1000    |      |
| Number of females               | 12                  |              | 12          | 12      | 12      |      |
| Observation of animals in cages |                     |              |             |         |         |      |
| Tonic convulsions               | Pre                 | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
| Mean (range)                    | Day 8               | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
|                                 | Day 15              | 1.0 (1)      | 1.0 (1)     | 1.0 (1) | 1.0 (1) |      |
|                                 | Day 1 of pregnancy  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 8 of pregnancy  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 15 of pregnancy | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |
|                                 | Day 3 of lactation  | 1.0 (1) [11] | 1.0 (1)     | 1.0 (1) | 1.0 (1) | [11] |

Figures in parentheses [ ] indicate number of females.

Findings were graded as follows

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions, 5: asphyxial convulsions.



Table 17-3 FOB of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

| Group                                     | Control             |         | bumetrizole |         |         |         |      |
|---|---------------------|---------|-------------|---------|---------|---------|------|
| mg/kg                                     | 0                   |         | 62.5        | 250     | 1000    |         |      |
| Number of females                         | 12                  |         | 12          | 12      | 12      |         |      |
| Observation of animals on observer's palm |                     |         |             |         |         |         |      |
| Ease of removal from cage                 | Pre                 | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |         |      |
|   | Mean (range)        |         |             |         |         |         |      |
| Ease of handling                          | Day 8               | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |         |      |
|   | Day 15              | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |         |      |
|   | Day 1 of pregnancy  | 2.0 (2) | [11]        | 2.0 (2) | 2.0 (2) | 2.0 (2) | [11] |
|   | Day 8 of pregnancy  | 2.0 (2) | [11]        | 2.0 (2) | 2.0 (2) | 2.0 (2) | [11] |
|   | Day 15 of pregnancy | 2.0 (2) | [11]        | 2.0 (2) | 2.0 (2) | 2.0 (2) | [11] |
|   | Day 3 of lactation  | 2.0 (2) | [11]        | 2.0 (2) | 2.0 (2) | 2.0 (2) | [11] |
|   | Pre                 | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |         |      |
|   | Mean (range)        |         |             |         |         |         |      |
| Muscle tone                               | Day 8               | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |         |      |
|   | Day 15              | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |         |      |
|   | Day 1 of pregnancy  | 2.0 (2) | [11]        | 2.0 (2) | 2.0 (2) | 2.0 (2) | [11] |
|   | Day 8 of pregnancy  | 2.0 (2) | [11]        | 2.0 (2) | 2.0 (2) | 2.0 (2) | [11] |
|   | Day 15 of pregnancy | 2.0 (2) | [11]        | 2.0 (2) | 2.0 (2) | 2.0 (2) | [11] |
|   | Day 3 of lactation  | 2.0 (2) | [11]        | 2.0 (2) | 2.0 (2) | 2.0 (2) | [11] |
|   | Pre                 | 2.0 (2) | 2.0 (2)     | 2.0 (2) | 2.0 (2) |         |      |
|   | Mean (range)        |         |             |         |         |         |      |
| Fur conditions                            | Day 8               | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |         |      |
|   | Day 15              | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |         |      |
|   | Day 1 of pregnancy  | 1.0 (1) | [11]        | 1.0 (1) | 1.0 (1) | 1.0 (1) | [11] |
|   | Day 8 of pregnancy  | 1.0 (1) | [11]        | 1.0 (1) | 1.0 (1) | 1.0 (1) | [11] |
|   | Day 15 of pregnancy | 1.0 (1) | [11]        | 1.0 (1) | 1.0 (1) | 1.0 (1) | [11] |
|   | Day 3 of lactation  | 1.0 (1) | [11]        | 1.0 (1) | 1.0 (1) | 1.0 (1) | [11] |
|   | Pre                 | 1.0 (1) | 1.0 (1)     | 1.0 (1) | 1.0 (1) |         |      |
|   | Mean (range)        |         |             |         |         |         |      |

Figures in parentheses [ ] indicate number of females.

Findings were graded as follows

- Ease of removal from cage 1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.  
Ease of handling 1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing, 3: struggling and trying to bite observer's hand.  
Muscle tone 1: Decreased, 2: normal, 3: increased.  
Fur conditions 1: Normal, 2: slightly soiled, 3: markedly soiled.