

Supplemental Table 2. Retinal atrophy in chronic safety studies: control animals-mouse

| CRO no. | Mouse strain | Housing conditions | | Illumination conditions | | | 6-month chronic toxicity study | | | | 2-year carcinogenicity study | | | |
|---------|--------------|--------------------|--------------------------|----------------------------------|---------------------------------------|-------------------------------------|--------------------------------|-------------------------------|--------------|-------------------|------------------------------|-------------------------------|--------------|-----------------------------|
| | | Cage type | Housing | Lighting intensity (Min-Max) lux | Height of measurement (m above floor) | 12 h Light-dark schedule (start at) | No. of studies (n) | Incidences of retinal atrophy | | rotation | No. of studies (n) | Incidences of retinal atrophy | | rotation |
| | | | | | | | | % of males | % of females | | | % of males | % of females | |
| 2 | CD-1 | plastic | group: max. 5 per cage | 325 | 1 | 7 a.m. | | | | | 9 | 4.1 (<9) | 3.5 (<7) | Monthly |
| 3 | CD-1 | plastic | group: 3 per cage | 250 – 650 | 1 | 6 a.m. | 60 | 2.8 | 2.8 | Mth., clw. (rack) | 21 | 11.7 | 15.3 | Mth., clw. (rack) |
| 4 | CD-1 | plastic | single | 300-450 | 1-2 | 5 a.m. | | | | | 5 | 4.4 | 5.9 | No |
| 5 | CD-1 | plastic | M: single, F: 3 per cage | 153 – 390 | 1 | 6 a.m. | 1 | 0 | 0 | No | 1 | 7 | 5 | Every 2 nd week |
| 1 | CD-1 | metal | | 270 – 430 | 0.7 – 1.5 | 5 a.m. | 3 | 0 | 1.5 | Mth., clw.** | 5 | 0 | 0 | Mth., clw. |
| 6 | CD-1 | metal | single | 181 – 798 | * | 7 a.m. | | | | | 2 | 5.8 | 9.2 | Every 6 th month |
| 8 | CD-1 | metal | single | 250 – 400 | 0.8 | 7 a.m. | | | | | 1 | 56 | 65 | No |
| 9 | CD-1 | metal | single or group | 150 – 600 | 0.85 | 6 a.m. | 1 | 0 | 0 | No | | | | |
| 3 | B6C3F1 | plastic | group: 3 per cage | 250 – 650 | 1 | 6 a.m. | 4 | 0 | 0 | Mth., clw. (rack) | 4 | 0.6 | 0.3 | Mth., clw. (rack) |
| 5 | B6C3F1 | plastic | group | 153 – 390 | 1 | 6 a.m. | | | | | 1 | 0 | 1 | Every 2 nd week |
| 6 | B6C3F1 / Crj | metal | single | 181 – 798 | * | 7 a.m. | | | | | 7 | 0.3 | 0.2 | Every 6 th month |
| 6 | JCl / B6C3F1 | metal | single | 181 – 798 | * | 7 a.m. | | | | | 10 | 0.2 | 0 | Every 6 th month |

| | | Housing conditions | | Illumination conditions | | | 6-month chronic toxicity study | | | | 2-year carcinogenicity study | | | |
|---------|---------------|--------------------|-----------------|------------------------------|-----------------------|--------------------------|--------------------------------|-------------------------------|--------------|----------|------------------------------|-------------------------------|--------------|----------|
| | | | | Lighting intensity (Min-Max) | Height of measurement | 12 h Light-dark schedule | No. of studies | Incidences of retinal atrophy | | | No. of studies | Incidences of retinal atrophy | | |
| CRO no. | Mouse strain | Cage type | Housing | lux | (m above floor) | (start at) | (n) | % of males | % of females | rotation | (n) | % of males | % of females | rotation |
| 8 | B6C3F1 / Crlj | metal | single | 250 – 400 | 0.8 | 7 a.m. | | | | | 1 | 0.9 | 0 | No |
| 9 | C57BL/6 | metal | single or group | 150 – 600 | 0.85 | 6 a.m. | | | | | 1 | 0 | 0 | No |
| 4 | NMRI | plastic | single | 300 – 450 | 1 – 2 | 5 a.m. | | | | | 15 | 0.37% | 0.85% | No |

*: measured directly underneath ceiling lamp; **: Mth. clw. = monthly clockwise; n.a. – not announced

Supplemental Table 3. Retinal atrophy in chronic safety studies: control animals-rat

| CRO no. | Rat strain | Housing condition | | Illumination conditions | | | 6-month chronic toxicity study | | | | 2-year carcinogenicity study | | | |
|---------|----------------|-------------------|--------------------------|----------------------------------|---------------------------------------|-------------------------------------|--------------------------------|-------------------------------|--------------|-------------------|------------------------------|-------------------------------|--------------|-----------------------------|
| | | Cage type | Housing | Lighting intensity (Min-Max) lux | Height of measurement (m above floor) | 12 h Light-dark schedule (start at) | No. of studies (n) | Incidences of retinal atrophy | | rotation | No. of studies (n) | Incidences of retinal atrophy | | rotation |
| | | | | | | | | % of males | % of females | | | % of males | % of females | |
| 1 | Wistar | metal | | 270 – 430 | 0.7 – 1.5 | 5 a.m. | 2 | 0 | 0 | Mth., clw.** | 1 | 24 | 51 | Mth., clw. |
| 2 | Wistar | plastic (IVC) | group: max. 2-3 per cage | 325 | 1 | 7 a.m. | 4 | 0 | 0 | Monthly (rack) | 3 | 10.8 (<13.3) | 6.3 (<11) | Monthly |
| 3 | Wistar | plastic | group: 5 per cage | 250 – 650 | 1 | 6 a.m. | 19 | 2.0 | 3.2 | Mth., clw. (rack) | 6 | 7.1 | 16.0 | Mth., clw. (rack) |
| 4 | Wistar | plastic | group: 3 or 5 per cage | 300 – 450 | 1 – 2 | 5 a.m. | 7 | 1.5 | 3.8 | No | 50 | 4.5 | 4.7 | No |
| 5 | Wistar | plastic | group: 4-5 per cage | 153 – 390 | 1 | 6 a.m. | 8 | 1 | 2 | No | 2 | 6 | 18 | Every 2 nd week |
| 1 | Sprague Dawley | metal | | 270 – 430 | 0.7 – 1.5 | 5 a.m. | 12 | 0 | 0 | Mth., clw. | 2 | 0 | 8 | Mth., clw. |
| 2 | Sprague Dawley | plastic (IVC) | group: max. 2-3 per cage | 325 | 1 | 7 a.m. | 5 | 2.8 (<6.7) | 1.4 (<5.6) | Monthly (rack) | 7 | 6.9 (<15.2) | 13.5 (<45) | Monthly (rack) |
| 6 | Sprague Dawley | metal | single | 99 – 736 | * | 7 a.m. | 62 | 2.1 | 1.8 | No | 13 | 21.1 | 37.9 | Every 6 th month |
| 8 | Sprague Dawley | metal | single | 250 – 400 | 0.8 | 7 a.m. | 8 | 5.6 | 6.3 | No | 1 | 7 | 8 | No |
| 9 | Sprague Dawley | metal | single or group | 150 – 600 | 0.85 | 6 a.m. | 15 | 0 | 0.6 | No | 2 | | | No |
| 3 | Sprague Dawley | plastic | group: 5 per cage | 250 – 650 | 1 | 6 a.m. | 42 | 0.1 | 0.8 | Mth., clw. (rack) | 26 | 2.5 | 3.0 | Mth., clw. (rack) |

| | | Housing condition | | Illumination conditions | | | 6-month chronic toxicity study | | | | 2-year carcinogenicity study | | | |
|---------|----------------|-------------------|---------------------|------------------------------|-----------------------|--------------------------|--------------------------------|-------------------------------|--------------|----------|------------------------------|-------------------------------|--------------|-----------------------------|
| | | | | Lighting intensity (Min-Max) | Height of measurement | 12 h Light-dark schedule | No. of studies | Incidences of retinal atrophy | | rotation | No. of studies | Incidences of retinal atrophy | | |
| CRO no. | Rat strain | Cage type | Housing | lux | (m above floor) | (start at) | (n) | % of males | % of females | rotation | (n) | % of males | % of females | rotation |
| 5 | Sprague Dawley | plastic | group: 4-5 per cage | 153 – 390 | 1 | 6 a.m. | 4 | 3 | 9 | No | | | | |
| 1 | Fischer | metal | | 270 – 430 | 0.7 – 1.5 | 5 a.m. | | | | | 1 | 0 | 0 | Mth., clw. |
| 6 | Fischer | metal | single | 99 – 736 | * | 7 a.m. | | | | | 16 | 69.5 | 72.8 | Every 6 th month |

*: measured directly underneath ceiling lamp; **: Mth. clw. = monthly clockwise