

Chemical: A Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

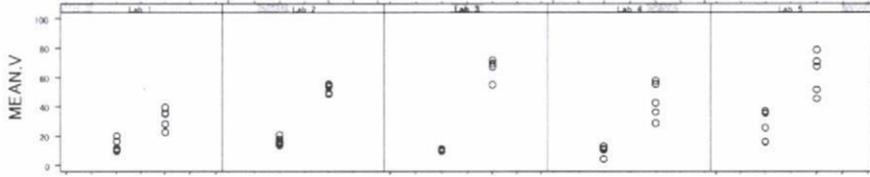


Fig. 2-SA

Table 2-SA

Chemical: A
Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Lab. | Variable | N | Vehicle | | | | EMS | | | | |
|------|------------|---|---------|------|------|------|------|------|------|------|------|
| | | | Mean | SD | Min | Max | Mean | SD | Min | Max | |
| 1 | id(MEAN V) | 5 | 13.6 | 4.4 | 9.9 | 20.1 | 5 | 32.2 | 6.8 | 22.6 | 39.8 |
| 2 | id(MEAN V) | 5 | 16.8 | 2.8 | 13.8 | 20.9 | 5 | 52.6 | 3.2 | 48.8 | 55.6 |
| 3 | id(MEAN V) | 5 | 10.8 | 0.7 | 9.7 | 11.4 | 5 | 66.6 | 6.7 | 54.9 | 72 |
| 4 | id(MEAN V) | 5 | 10.1 | 3.3 | 4.4 | 12.9 | 5 | 44.2 | 12.3 | 28.8 | 57.5 |
| 5 | id(MEAN V) | 5 | 26 | 10.1 | 15.9 | 37 | 5 | 62.9 | 13.8 | 45.7 | 78.9 |

Chemical: A Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

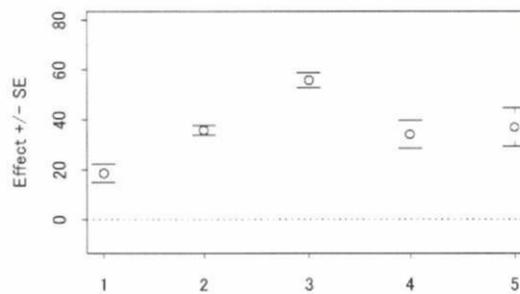


Fig. 3-SA

Chemical: A
Organ: Stomach Parameter: PCT tail DNA
Transformation: id Link: id

Table 3-SA

| Lab. | Variable | Effect | SE | L95% | U95% | Method | | | | | |
|------|------------|--------|------|-------|-------|--------|----------|---------------|---------|----------|---|
| | | | | | | Pooled | | Satterthwaite | | | |
| | | | | | | df | P-value | df | P-value | | |
| 1 | id(MEAN V) | 18.58 | 3.63 | 10.22 | 26.95 | 8 | 9.00E-04 | 1 | 6.85 | 0.001 | 1 |
| 2 | id(MEAN V) | 35.83 | 1.91 | 31.43 | 40.23 | 8 | 6.70E-08 | 1 | 7.83 | 8.60E-08 | 1 |
| 3 | id(MEAN V) | 55.78 | 3.03 | 48.8 | 62.76 | 8 | 7.70E-08 | 1 | 4.09 | 4.30E-05 | 1 |
| 4 | id(MEAN V) | 34.09 | 5.7 | 20.94 | 47.23 | 8 | 3.30E-04 | 1 | 4.57 | 0.003 | 1 |
| 5 | id(MEAN V) | 36.9 | 7.64 | 19.29 | 54.52 | 8 | 0.001 | 1 | 7.34 | 0.002 | 1 |

For the calculation for CIs the pooled method were used

Chemical: A Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

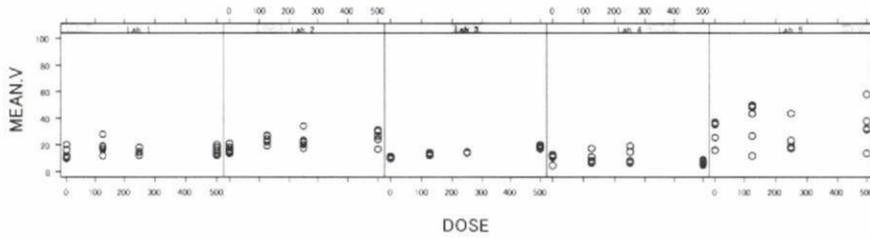


Fig. 4-SA

Table 4-SA

Chemical: A
Organ: Stomach Endpoint: Tail length
Transformation: id Link: id

| Lab | Variable | Group | | | | | | | | | | | | | | | | | | | | | | | |
|-----|------------|---------|---|------|------|------|------|------|---|------|------|--------|------|------|---|------|------|------|------|------|---|------|------|------|------|
| | | Vehicle | | | | | Low | | | | | Medium | | | | | High | | | | | | | | |
| | | Dose | N | Mean | SD | Min | Max | Dose | N | Mean | SD | Min | Max | Dose | N | Mean | SD | Min | Max | Dose | N | Mean | SD | Min | Max |
| 1 | id(MEAN_V) | 0 | 5 | 0 | 0 | 0 | 0.1 | 125 | 5 | 0.1 | 0 | 0 | 0.1 | 250 | 5 | 0.1 | 0 | 0 | 0.1 | 500 | 5 | 0.1 | 0 | 0 | 0.1 |
| 2 | id(MEAN_V) | 0 | 5 | 84.8 | 12.1 | 71.3 | 104 | 125 | 5 | 81.6 | 9.3 | 73.1 | 95.8 | 250 | 5 | 87.3 | 8.9 | 77.4 | 97.6 | 500 | 5 | 75.7 | 11.4 | 60 | 88.3 |
| 3 | id(MEAN_V) | 0 | 5 | 65.2 | 12.3 | 51.3 | 80.2 | 125 | 5 | 92.2 | 12.8 | 75.4 | 105 | 250 | 5 | 79 | 20.7 | 45.3 | 103 | 500 | 5 | 102 | 19.1 | 71.5 | 119 |
| 4 | id(MEAN_V) | 0 | 5 | 35.8 | 5.4 | 29.8 | 41.3 | 125 | 5 | 40.7 | 7.7 | 32.8 | 51.8 | 250 | 5 | 41.8 | 12.7 | 26.7 | 55.2 | 500 | 5 | 33.4 | 3.4 | 29.5 | 37.6 |
| 5 | id(MEAN_V) | 0 | 5 | 54.6 | 18.2 | 34.7 | 83.9 | 125 | 5 | 59.4 | 10.9 | 49.4 | 77.9 | 250 | 5 | 55.2 | 16.9 | 39.7 | 83 | 500 | 5 | 63.9 | 16.9 | 43.1 | 88.6 |

Chemical: A Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

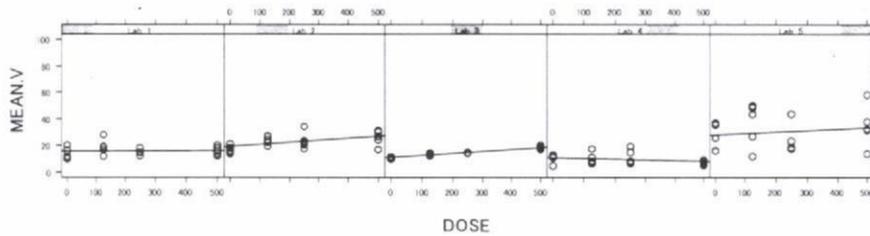


Fig. 5-SA

Table 5-SA Chemical: A
Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Lab. | Variable | Slope | SE | L95% | U95% | P-value | J_LI |
|------|------------|--------|-------|--------|--------|----------|------|
| 1 | id(MEAN_V) | 0.0015 | 0.005 | -0.01 | 0.0127 | 0.789 | 0 |
| 2 | id(MEAN_V) | 0.0151 | 0.006 | 0.0024 | 0.0277 | 0.022 | 1 |
| 3 | id(MEAN_V) | 0.0142 | 0.001 | 0.0122 | 0.0163 | 2.00E-11 | 1 |
| 4 | id(MEAN_V) | -0.006 | 0.005 | -0.016 | 0.0043 | 0.247 | 0 |
| 5 | id(MEAN_V) | 0.0106 | 0.017 | -0.025 | 0.0459 | 0.535 | 0 |

Chemical: A Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

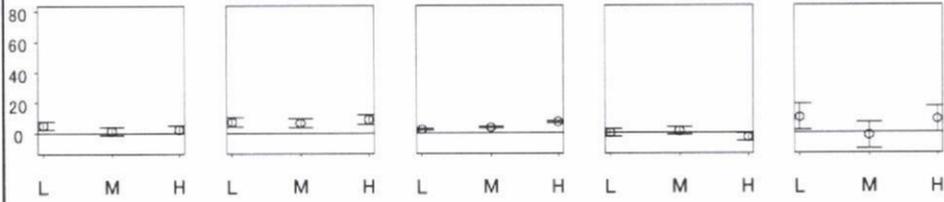


Fig. 6-SA

Table 6-SA

Chemical: A
Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Lab | Variable | V - L | | | | V - M | | | | V - H | | | | J D | J L | | | |
|-----|-----------|--------|----|------|----------|----------|--------|----|------|----------|----------|--------|----|------|----------|----------|----------|-----|
| | | Effect | df | SE | Dunnnett | LSD | Effect | df | SE | Dunnnett | LSD | Effect | df | | | SE | Dunnnett | LSD |
| 1 | id:MEAN V | 5.21 | 16 | 2.65 | 0.079 | 0.033 | 1.32 | 16 | 2.65 | 0.545 | 0.312 | 2.3 | 16 | 2.65 | 0.385 | 0.199 | 0 | 1 |
| 2 | id:MEAN V | 7.24 | 16 | 3.04 | 0.038 | 0.015 | 6.6 | 16 | 3.04 | 0.055 | 0.023 | 9 | 16 | 3.04 | 0.012 | 0.005 | 1 | 1 |
| 3 | id:MEAN V | 2.44 | 16 | 0.52 | 3.10E-04 | 1.10E-04 | 3.73 | 16 | 0.52 | 2.90E-06 | 1.00E-06 | 7.31 | 16 | 0.52 | 3.00E-10 | 9.00E-11 | 1 | 1 |
| 4 | id:MEAN V | -0.21 | 16 | 2.53 | 0.778 | 0.532 | 1.09 | 16 | 2.53 | 0.575 | 0.336 | -2.96 | 16 | 2.53 | 0.974 | 0.87 | 0 | 0 |
| 5 | id:MEAN V | 10.02 | 16 | 8.66 | 0.274 | 0.132 | -1.83 | 16 | 8.66 | 0.819 | 0.582 | 8.71 | 16 | 8.66 | 0.33 | 0.165 | 0 | 0 |

One side tests were performed

Chemical: B , Endpoint: PCT tail DNA, Transformation: id, Organ: Stomach

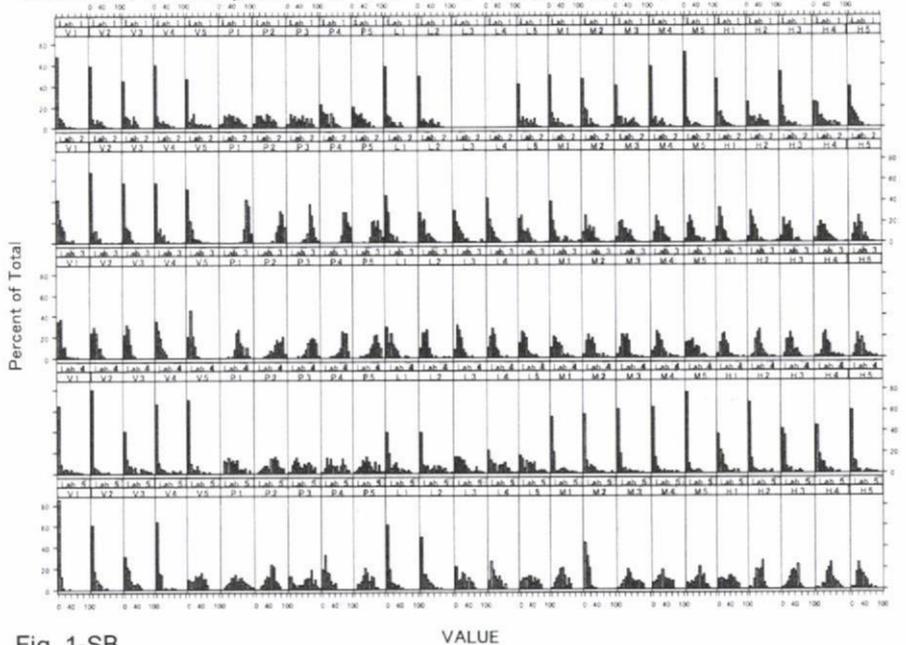


Fig. 1-SB

Table 1-SB

Chemical: B
 Organ: Stomach Endpoint: PCT Tail DNA Transformation: id

| Lab. | Vehicle | | | | | EMS | | | | | Control | | | | | Protein | | | | | High | | | | | | | | | | | | | |
|------|---------|------|-----|------|---|------|------|------|------|---|---------|------|-----|------|---|---------|------|------|------|---|------|------|------|------|---|------|------|-----|------|---|------|------|------|------|
| | Mean | SD | Min | Max | N | Mean | SD | Min | Max | N | Mean | SD | Min | Max | N | Mean | SD | Min | Max | N | Mean | SD | Min | Max | N | Mean | SD | Min | Max | | | | | |
| 1 | 12.6 | 4.1 | 7.2 | 17.9 | 5 | 32.8 | 8.7 | 23.2 | 40.8 | 5 | 10 | 1.6 | 8.2 | 11.7 | 5 | 69.6 | 5.9 | 59.3 | 73.4 | 5 | 45.1 | 7.1 | 36.7 | 55.5 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 41.1 | 14.7 | 15.7 | 50.8 |
| 2 | 10 | 1.6 | 8.2 | 11.7 | 5 | 80.8 | 5.7 | 73.8 | 85.9 | 5 | 12 | 1.1 | 11 | 13.8 | 5 | 69.6 | 5.9 | 59.3 | 73.4 | 5 | 45.1 | 7.1 | 36.7 | 55.5 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 41.1 | 14.7 | 15.7 | 50.8 |
| 3 | 12 | 1.1 | 11 | 13.8 | 5 | 69.6 | 5.9 | 59.3 | 73.4 | 5 | 12 | 1.1 | 11 | 13.8 | 5 | 45.1 | 7.1 | 36.7 | 55.5 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 41.1 | 14.7 | 15.7 | 50.8 |
| 4 | 12.2 | 6.5 | 5.6 | 22.8 | 5 | 45.1 | 7.1 | 36.7 | 55.5 | 5 | 12.2 | 6.5 | 5.6 | 22.8 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 41.1 | 14.7 | 15.7 | 50.8 |
| 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 41.1 | 14.7 | 15.7 | 50.8 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 41.1 | 14.7 | 15.7 | 50.8 |

Chemical: B Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

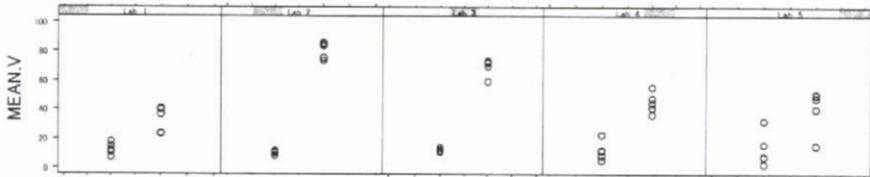


Fig. 2-SB

Table 2-SB

Chemical: B
 Organ: Stomach Endpoint: PCT tail DNA
 Transformation: id Link: id

| Lab. | Variable | Vehicle | | | | EMS | | | | | |
|------|------------|---------|------|------|-----|------|---|------|------|------|------|
| | | N | Mean | SD | Min | Max | N | Mean | SD | Min | Max |
| 1 | id(MEAN V) | 5 | 12.6 | 4.1 | 7.2 | 17.9 | 5 | 32.8 | 8.7 | 23.2 | 40.8 |
| 2 | id(MEAN V) | 5 | 10 | 1.6 | 8.2 | 11.7 | 5 | 80.8 | 5.7 | 73.8 | 85.9 |
| 3 | id(MEAN V) | 5 | 12 | 1.1 | 11 | 13.8 | 5 | 69.6 | 5.9 | 59.3 | 73.4 |
| 4 | id(MEAN V) | 5 | 12.2 | 6.5 | 5.6 | 22.8 | 5 | 45.1 | 7.1 | 36.7 | 55.5 |
| 5 | id(MEAN V) | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 5 | 41.1 | 14.7 | 15.7 | 50.8 |

Chemical: B Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

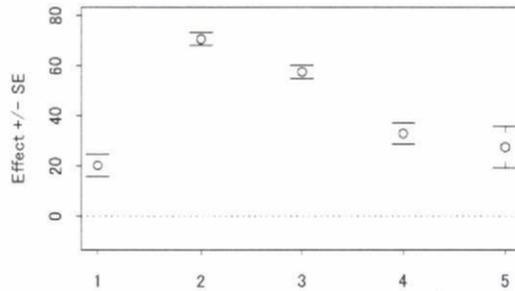


Fig. 3-SB

Chemical: B
Organ: Stomach Parameter: PCT tail DNA
Transformation: id Link: id

Table 3-SB

| Lab. | Variable | Effect | SE | L95% | U95% | df | Method | | | | | |
|------|-------------|--------|------|-------|-------|----|----------|---|------|---------------|---------|---|
| | | | | | | | Pooled | | | Satterthwaite | | |
| | | | | | | | P-value | J | T | df | P-value | J |
| 1 | id (MEAN V) | 20.23 | 4.31 | 10.28 | 30.17 | 8 | 0.002 | 1 | 5.65 | 0.004 | 1 | |
| 2 | id (MEAN V) | 70.81 | 2.63 | 64.75 | 76.87 | 8 | 4.00E-09 | 1 | 4.6 | 3.10E-06 | 1 | |
| 3 | id (MEAN V) | 57.61 | 2.69 | 51.4 | 63.82 | 8 | 2.40E-08 | 1 | 4.27 | 1.70E-05 | 1 | |
| 4 | id (MEAN V) | 32.95 | 4.3 | 23.03 | 42.87 | 8 | 6.00E-05 | 1 | 7.95 | 6.20E-05 | 1 | |
| 5 | id (MEAN V) | 27.58 | 8.4 | 8.22 | 46.94 | 8 | 0.011 | 1 | 7.58 | 0.012 | 1 | |

For the calculation for CIs the pooled method were used

Chemical: B Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

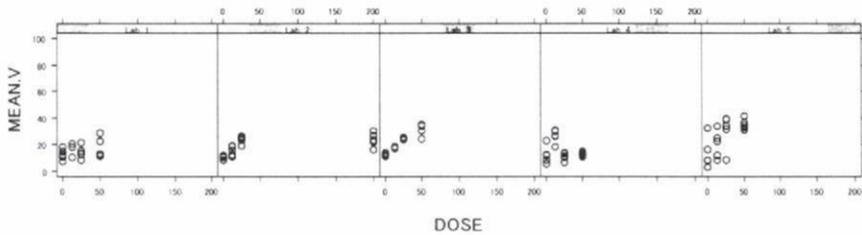


Fig. 4-SB

Table 4-SB

Chemical: B
Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Lab. | Variable | Dose | N | Vehicle | | Group | | | | | | | | | | | | | | | | | | | |
|------|-------------|------|---|---------|------|-------|------|------|----|--------|------|------|------|------|----|------|------|------|------|------|----|------|-----|------|------|
| | | | | Mean | SD | Low | | | | Medium | | | | High | | | | | | | | | | | |
| | | | | Min | Max | Dose | N | Mean | SD | Min | Max | Dose | N | Mean | SD | Min | Max | Dose | N | Mean | SD | Min | Max | | |
| 1 | id (MEAN V) | 0 | 5 | 12.6 | 4.1 | 7.2 | 17.9 | 12.5 | 3 | 16.3 | 5.3 | 10.4 | 20.6 | 25 | 5 | 14.2 | 4.8 | 8.3 | 21.4 | 50 | 5 | 17.7 | 7.6 | 11.2 | 28.8 |
| 2 | id (MEAN V) | 0 | 5 | 10 | 1.6 | 8.2 | 11.7 | 12.5 | 5 | 15.2 | 3.6 | 10.8 | 18.8 | 25 | 5 | 23.7 | 2.9 | 18.9 | 26.2 | 200 | 5 | 23.8 | 5.4 | 16.2 | 30.4 |
| 3 | id (MEAN V) | 0 | 5 | 12 | 1.1 | 11 | 13.8 | 12.5 | 5 | 18 | 0.8 | 17 | 18.6 | 25 | 5 | 24.5 | 0.8 | 23.5 | 25.5 | 50 | 5 | 31.7 | 4.5 | 24.3 | 35.1 |
| 4 | id (MEAN V) | 0 | 5 | 12.2 | 6.5 | 5.6 | 22.8 | 12.5 | 5 | 26.4 | 5 | 18.4 | 30.7 | 25 | 5 | 11 | 2.9 | 6.6 | 14 | 50 | 5 | 12.7 | 1.5 | 10.8 | 14.7 |
| 5 | id (MEAN V) | 0 | 5 | 13.5 | 11.6 | 2.9 | 32.4 | 12.5 | 5 | 20.2 | 10.3 | 8.2 | 33.8 | 25 | 5 | 30.4 | 12.7 | 8.3 | 39.3 | 50 | 5 | 35.3 | 4 | 31.1 | 41.5 |

Chemical: B Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

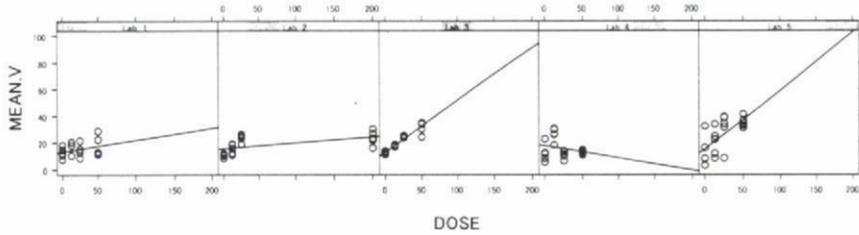


Fig. 5-SB

Table 5-SB Chemical: B
Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Lab. | Variable | Slope | SE | L95% | U95% | P-value | J LI |
|------|------------|--------|-------|--------|--------|----------|------|
| 1 | id(MEAN V) | 0.0896 | 0.066 | -0.051 | 0.2302 | 0.196 | 0 |
| 2 | id(MEAN V) | 0.0459 | 0.016 | 0.0122 | 0.0796 | 0.01 | 1 |
| 3 | id(MEAN V) | 0.3926 | 0.03 | 0.3287 | 0.4564 | 2.00E-10 | 1 |
| 4 | id(MEAN V) | -0.09 | 0.092 | -0.284 | 0.1039 | 0.342 | 0 |
| 5 | id(MEAN V) | 0.4398 | 0.121 | 0.1859 | 0.6938 | 0.002 | 1 |

Chemical: B Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

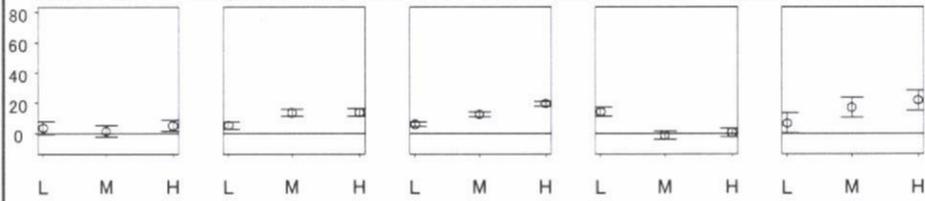


Fig. 6-SB

Table 6-SB

Chemical: B
Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Lab. | Variable | V-L | | | | V-M | | | | V-H | | | | J D | J L | | | |
|------|------------|--------|----|------|----------|----------|--------|----|------|----------|----------|--------|----|------|----------|----------|----------|-----|
| | | Effect | df | SE | Dunnnett | LSD | Effect | df | SE | Dunnnett | LSD | Effect | df | | | SE | Dunnnett | LSD |
| 1 | id(MEAN V) | 3.72 | 14 | 4.12 | 0.371 | 0.191 | 1.61 | 14 | 3.57 | 0.567 | 0.33 | 5.13 | 14 | 3.57 | 0.189 | 0.086 | 0 | 0 |
| 2 | id(MEAN V) | 5.3 | 16 | 2.29 | 0.043 | 0.017 | 13.71 | 16 | 2.29 | 2.80E-05 | 9.70E-06 | 13.83 | 16 | 2.29 | 2.50E-05 | 8.80E-06 | 1 | 1 |
| 3 | id(MEAN V) | 6 | 16 | 1.5 | 0.001 | 5.20E-04 | 12.51 | 16 | 1.5 | 4.60E-07 | 1.60E-07 | 19.69 | 16 | 1.5 | 8.00E-10 | 3.00E-10 | 1 | 1 |
| 4 | id(MEAN V) | 14.26 | 16 | 2.79 | 1.50E-04 | 5.30E-05 | -1.12 | 16 | 2.79 | 0.87 | 0.654 | 0.5 | 16 | 2.79 | 0.681 | 0.43 | 1 | 1 |
| 5 | id(MEAN V) | 6.73 | 16 | 6.47 | 0.316 | 0.157 | 16.88 | 16 | 6.47 | 0.024 | 0.01 | 21.75 | 16 | 6.47 | 0.005 | 0.002 | 1 | 1 |

One side tests were performed

Chemical: C , Endpoint: PCT tail DNA, Transformation: id, Organ: Stomach

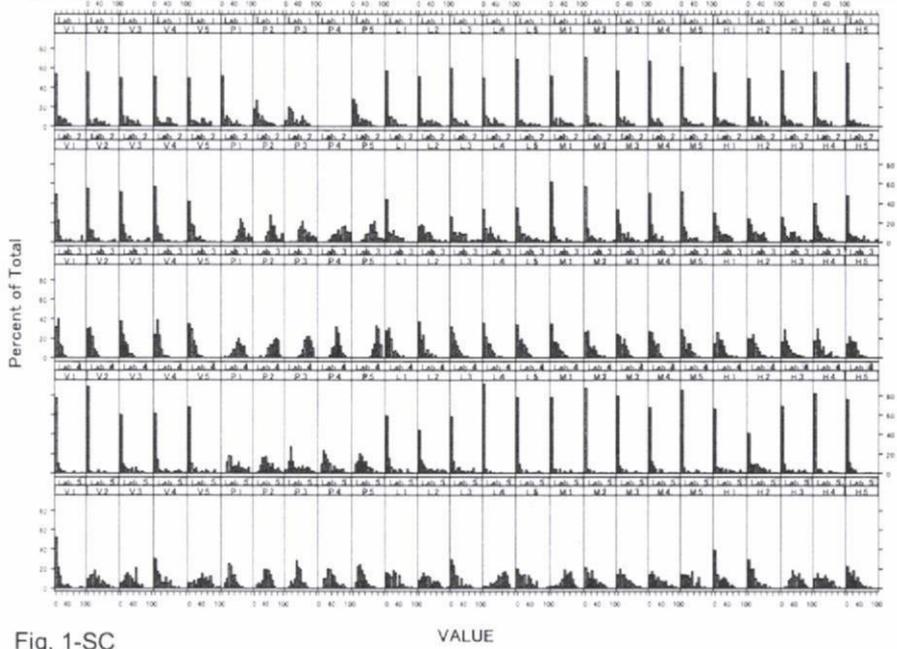


Fig. 1-SC

Table 1-SC

Chemical: C
Organ: Stomach
Endpoint: PCT tail DNA
Transformation: id

| Lab | Vehicle | | | | | | | | | | Dose | | | | | | | | | | | | | | | | |
|-----|---------|------|------|------|------|------|-------|------|------|------|------|------|-------|------|------|------|------|------|-------|------|------|------|------|------|------|------|------|
| | Group | N | Mean | SD | Min | Max | Group | N | Mean | SD | Min | Max | Group | N | Mean | SD | Min | Max | Group | N | Mean | SD | Min | Max | | | |
| 1 | 0.000 | 11 | 4.8 | 14.4 | 0.0 | 53.3 | 200 | 100 | 15.1 | 9.20 | 0.0 | 98.2 | 120 | 100 | 11.0 | 2.8 | 15.4 | 0.0 | 85.5 | 250 | 100 | 17.3 | 9.8 | 22.0 | 0.0 | 73.0 | |
| 2 | 0.000 | 12 | 3.0 | 20.1 | 0.0 | 89.4 | 200 | 100 | 22.9 | 17.9 | 10.0 | 0.0 | 120 | 100 | 13.0 | 2.1 | 24.1 | 0.0 | 95.0 | 250 | 100 | 7.6 | 0.0 | 46.0 | 0.0 | 85.0 | |
| 3 | 0.000 | 12 | 5.5 | 19.4 | 0.0 | 85.0 | 200 | 100 | 23.0 | 21.0 | 0.0 | 111 | 120 | 100 | 12.0 | 2.2 | 17.0 | 0.0 | 88.0 | 250 | 100 | 12.0 | 3.0 | 18.0 | 0.0 | 93.0 | |
| 4 | 0.000 | 12 | 5.1 | 21.4 | 0.0 | 82.0 | 200 | 100 | 22.0 | 21.0 | 0.0 | 110 | 120 | 100 | 15.7 | 5.8 | 15.7 | 0.0 | 88.0 | 250 | 100 | 8.2 | 0.0 | 12.0 | 0.0 | 44.0 | |
| 5 | 0.000 | 12 | 6.9 | 23.0 | 0.0 | 87.0 | 200 | 100 | 18.4 | 11.0 | 18.0 | 0.0 | 81.0 | 120 | 100 | 10.0 | 11.0 | 17.0 | 0.0 | 73.0 | 250 | 100 | 12.4 | 8.0 | 9.0 | 0.0 | 83.0 |
| 6 | 0.000 | 17.0 | 6.0 | 27.0 | 0.0 | 86.0 | 200 | 100 | 69.1 | 67.5 | 14.0 | 0.0 | 98.0 | 18.0 | 9.0 | 18.0 | 0.0 | 80.0 | 250 | 100 | 20.0 | 2.0 | 20.0 | 0.0 | 58.0 | | |
| 7 | 0.000 | 14.4 | 4.5 | 22.0 | 0.0 | 91.0 | 200 | 100 | 65.8 | 67.0 | 14.0 | 43.0 | 97.0 | 120 | 100 | 25.0 | 19.0 | 27.0 | 0.0 | 93.0 | 250 | 100 | 13.0 | 4.0 | 20.0 | 0.0 | 88.0 |
| 8 | 0.000 | 15.0 | 5.8 | 23.0 | 0.0 | 91.0 | 200 | 100 | 62.4 | 56.0 | 14.0 | 19.0 | 88.0 | 120 | 100 | 18.0 | 14.0 | 24.0 | 0.0 | 98.0 | 250 | 100 | 12.0 | 2.0 | 12.0 | 0.0 | 89.0 |
| 9 | 0.000 | 16.0 | 7.0 | 15.0 | 0.0 | 88.4 | 200 | 100 | 77.0 | 78.0 | 13.0 | 23.0 | 93.0 | 120 | 100 | 13.0 | 14.0 | 18.0 | 0.0 | 79.0 | 250 | 100 | 13.4 | 5.0 | 18.0 | 0.0 | 84.4 |
| 10 | 0.000 | 12.0 | 7.0 | 18.0 | 0.0 | 84.0 | 200 | 100 | 83.8 | 84.0 | 14.0 | 23.0 | 98.0 | 120 | 100 | 27.0 | 11.4 | 27.0 | 0.0 | 84.0 | 250 | 100 | 17.0 | 3.0 | 18.0 | 0.0 | 80.0 |
| 11 | 0.000 | 10.0 | 9.0 | 7.0 | 0.0 | 86.0 | 200 | 100 | 54.0 | 55.0 | 14.0 | 10.0 | 81.0 | 120 | 100 | 17.0 | 17.0 | 17.4 | 0.0 | 80.0 | 250 | 100 | 14.0 | 11.0 | 12.0 | 0.0 | 81.0 |
| 12 | 0.000 | 11.8 | 10.0 | 8.0 | 0.0 | 84.0 | 200 | 100 | 68.4 | 70.8 | 13.0 | 21.0 | 97.0 | 120 | 100 | 13.0 | 11.0 | 17.0 | 0.0 | 93.0 | 250 | 100 | 18.0 | 11.0 | 14.0 | 0.0 | 80.0 |
| 13 | 0.000 | 11.8 | 8.8 | 8.0 | 0.0 | 86.0 | 200 | 100 | 72.0 | 72.0 | 10.0 | 25.0 | 97.0 | 120 | 100 | 14.0 | 8.0 | 11.0 | 0.0 | 84.0 | 250 | 100 | 18.0 | 17.0 | 11.0 | 0.0 | 87.0 |
| 14 | 0.000 | 11.5 | 10.0 | 10.0 | 0.0 | 81.0 | 200 | 100 | 55.0 | 55.0 | 10.0 | 20.0 | 88.0 | 120 | 100 | 13.4 | 10.0 | 11.0 | 0.0 | 87.0 | 250 | 100 | 14.2 | 10.0 | 10.0 | 0.0 | 81.0 |
| 15 | 0.000 | 10.0 | 9.0 | 9.0 | 0.0 | 84.0 | 200 | 100 | 78.4 | 78.0 | 10.0 | 20.0 | 88.0 | 120 | 100 | 14.0 | 12.4 | 11.0 | 0.0 | 86.0 | 250 | 100 | 15.0 | 13.0 | 13.0 | 0.0 | 87.0 |
| 16 | 0.000 | 6.0 | 10.0 | 14.0 | 0.0 | 88.0 | 200 | 100 | 63.0 | 37.0 | 27.0 | 13.0 | 93.0 | 120 | 100 | 12.4 | 8.0 | 10.0 | 0.0 | 80.0 | 250 | 100 | 9.0 | 8.0 | 20.0 | 0.0 | 88.0 |
| 17 | 0.000 | 4.5 | 0.4 | 12.0 | 0.0 | 87.0 | 200 | 100 | 46.0 | 47.0 | 18.0 | 11.0 | 83.0 | 120 | 100 | 20.0 | 8.0 | 26.4 | 0.0 | 92.0 | 250 | 100 | 4.8 | 0.0 | 12.0 | 0.0 | 88.0 |
| 18 | 0.000 | 13.0 | 2.4 | 3.0 | 0.0 | 86.4 | 200 | 100 | 34.0 | 25.0 | 24.0 | 1.0 | 85.0 | 120 | 100 | 15.0 | 3.0 | 24.0 | 0.0 | 87.0 | 250 | 100 | 8.0 | 0.0 | 14.0 | 0.0 | 81.4 |
| 19 | 0.000 | 19.0 | 7.0 | 24.0 | 0.0 | 88.4 | 200 | 100 | 35.4 | 24.0 | 19.0 | 7.0 | 90.4 | 120 | 100 | 7.4 | 0.0 | 7.0 | 0.0 | 87.0 | 250 | 100 | 3.0 | 0.0 | 18.0 | 0.0 | 81.0 |
| 20 | 0.000 | 11.4 | 21.0 | 0.0 | 84.0 | 200 | 100 | 39.4 | 29.0 | 18.0 | 2.4 | 93.0 | 120 | 100 | 7.0 | 0.0 | 16.0 | 0.0 | 79.0 | 250 | 100 | 5.0 | 0.0 | 14.0 | 0.0 | 80.0 | |
| 21 | 0.000 | 1.0 | 1.0 | 0.0 | 80.4 | 200 | 100 | 71.0 | 26.0 | 7.4 | 8.0 | 93.4 | 120 | 100 | 24.0 | 22.0 | 7.0 | 0.0 | 83.0 | 250 | 100 | 49.4 | 50.0 | 7.0 | 0.0 | 80.0 | |
| 22 | 0.000 | 20.0 | 23.0 | 19.0 | 0.0 | 84.0 | 200 | 100 | 42.0 | 43.0 | 17.0 | 8.0 | 93.4 | 120 | 100 | 22.0 | 21.0 | 0.0 | 82.4 | 250 | 100 | 22.0 | 21.0 | 18.0 | 0.0 | 81.0 | |
| 23 | 0.000 | 30.0 | 31.0 | 17.0 | 0.0 | 88.0 | 200 | 100 | 40.0 | 40.0 | 13.0 | 12.4 | 87.0 | 120 | 100 | 17.0 | 12.0 | 0.0 | 89.0 | 250 | 100 | 24.0 | 20.0 | 18.0 | 0.0 | 86.0 | |
| 24 | 0.000 | 19.0 | 13.4 | 19.0 | 0.0 | 86.0 | 200 | 100 | 38.0 | 38.0 | 13.4 | 14.0 | 89.0 | 120 | 100 | 15.0 | 16.4 | 15.4 | 0.0 | 85.4 | 250 | 100 | 20.0 | 21.0 | 22.0 | 0.0 | 81.0 |
| 25 | 0.000 | 44.0 | 44.0 | 21.0 | 0.0 | 85.0 | 200 | 100 | 27.0 | 25.0 | 17.4 | 8.0 | 90.0 | 120 | 100 | 25.0 | 21.0 | 20.0 | 0.0 | 97.0 | 250 | 100 | 28.0 | 23.0 | 18.4 | 0.0 | 86.0 |

Chemical: C Endpoint: PCT Tail DNA Transformation: id Organ: Stomach



Fig. 2-SC

Table 2-SC

Chemical: C
Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Lab. | Variable | N | Vehicle | | | | EMS | | | | |
|------|------------|---|---------|------|------|------|------|------|-----|------|------|
| | | | Mean | SD | Min | Max | Mean | SD | Min | Max | |
| 1 | id(MEAN V) | 5 | 16.1 | 2.9 | 11.8 | 19.4 | 4 | 21.7 | 6.3 | 15.1 | 29.9 |
| 2 | id(MEAN V) | 5 | 14.3 | 2.5 | 10.7 | 17.7 | 5 | 66.5 | 3.8 | 62.6 | 71.7 |
| 3 | id(MEAN V) | 5 | 11.1 | 0.7 | 10.1 | 11.8 | 5 | 67 | 9.3 | 56.1 | 78.4 |
| 4 | id(MEAN V) | 5 | 10.2 | 4.6 | 4.5 | 15.2 | 5 | 37.8 | 6.5 | 32.4 | 46 |
| 5 | id(MEAN V) | 5 | 27.3 | 12.7 | 11 | 44.1 | 5 | 36.2 | 6.4 | 27.9 | 42.9 |

Chemical: C Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

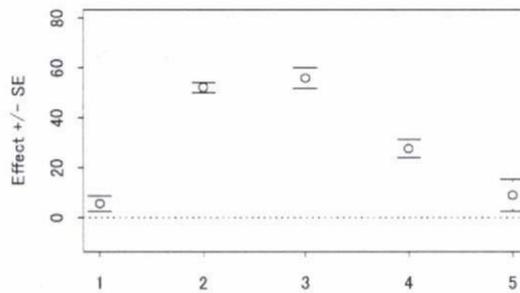


Fig. 3-SC

Chemical: C
Organ: Stomach Parameter: PCT tail DNA
Transformation: id Link: id

Table 3-SC

| Lab. | Variable | Effect | SE | L95% | U95% | df | Method | | | | |
|------|------------|--------|------|-------|-------|---------|----------|----|---------------|----------|---|
| | | | | | | | Pooled | | Satterthwaite | | |
| | | | | | | P-value | J T | df | P-value | J T | |
| 1 | id(MEAN V) | 5.63 | 3.11 | -1.73 | 13 | 7 | 0.113 | 0 | 4.02 | 0.171 | 0 |
| 2 | id(MEAN V) | 52.22 | 2.05 | 47.49 | 56.95 | 8 | 6.00E-09 | 1 | 6.97 | 3.90E-08 | 1 |
| 3 | id(MEAN V) | 55.92 | 4.19 | 46.27 | 65.58 | 8 | 9.40E-07 | 1 | 4.04 | 1.70E-04 | 1 |
| 4 | id(MEAN V) | 27.66 | 3.57 | 19.42 | 35.9 | 8 | 5.50E-05 | 1 | 7.22 | 9.50E-05 | 1 |
| 5 | id(MEAN V) | 8.87 | 6.36 | -5.78 | 23.53 | 8 | 0.2 | 0 | 5.9 | 0.213 | 0 |

For the calculation for CIs the pooled method were used.

Chemical: C Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

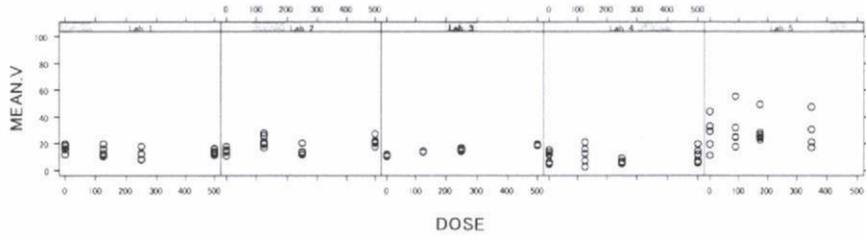


Fig. 4-SC

Table 4-SC

Chemical: C
Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Lab. | Variable | Dose | N | Group | | | | | | | | | | | | | | | | | | | | | |
|------|------------|------|---|---------|------|------|------|------|---|------|------|--------|------|------|---|------|------|------|------|------|---|------|-----|------|------|
| | | | | Vehicle | | | | Low | | | | Medium | | | | High | | | | | | | | | |
| | | | | Mean | SD | Min | Max | Dose | N | Mean | SD | Min | Max | Dose | N | Mean | SD | Min | Max | Dose | N | Mean | SD | Min | Max |
| 1 | id(MEAN V) | 0 | 5 | 16.1 | 2.9 | 11.8 | 19.4 | 125 | 5 | 13.8 | 3.9 | 10.2 | 19.6 | 250 | 5 | 11.6 | 4 | 7.6 | 17.7 | 500 | 5 | 13.9 | 2.1 | 11.1 | 16.2 |
| 2 | id(MEAN V) | 0 | 5 | 14.3 | 2.5 | 10.7 | 17.7 | 125 | 5 | 22.2 | 4.6 | 16.7 | 28 | 250 | 5 | 14.4 | 3.3 | 11.6 | 20.2 | 500 | 5 | 21.7 | 3.6 | 17.6 | 27.4 |
| 3 | id(MEAN V) | 0 | 5 | 11.1 | 0.7 | 10.1 | 11.8 | 125 | 5 | 13.7 | 0.3 | 13.4 | 14.1 | 250 | 5 | 15.7 | 1.1 | 14.2 | 16.6 | 500 | 5 | 19 | 0.5 | 18.3 | 19.6 |
| 4 | id(MEAN V) | 0 | 5 | 10.2 | 4.6 | 4.5 | 15.2 | 125 | 5 | 11.7 | 7.2 | 2.3 | 20.8 | 250 | 5 | 7.1 | 1.9 | 4.9 | 9.1 | 500 | 5 | 11.7 | 5.8 | 5.5 | 19.7 |
| 5 | id(MEAN V) | 0 | 5 | 27.3 | 12.7 | 11 | 44.1 | 87.5 | 5 | 30.9 | 14.7 | 17.5 | 55.6 | 175 | 5 | 30.2 | 10.9 | 22.9 | 49.4 | 350 | 5 | 26.7 | 13 | 16.9 | 47.6 |

Chemical: C Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

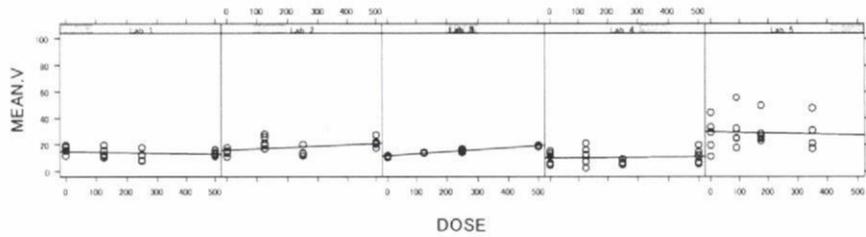


Fig. 5-SC

Table 5-SCB Chemical: C
Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Lab. | Variable | Slope | SE | L95% | U95% | P-value | J LI |
|------|------------|--------|----------|--------|--------|----------|------|
| 1 | id(MEAN V) | -0.004 | 0.004 | -0.013 | 0.0049 | 0.365 | 0 |
| 2 | id(MEAN V) | 0.0099 | 0.006 | -0.003 | 0.0223 | 0.111 | 0 |
| 3 | id(MEAN V) | 0.0155 | 9.10E-04 | 0.0136 | 0.0174 | 2.00E-12 | 1 |
| 4 | id(MEAN V) | 0.0013 | 0.006 | -0.012 | 0.0149 | 0.838 | 0 |
| 5 | id(MEAN V) | -0.005 | 0.021 | -0.049 | 0.0401 | 0.834 | 0 |

Chemical: C Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

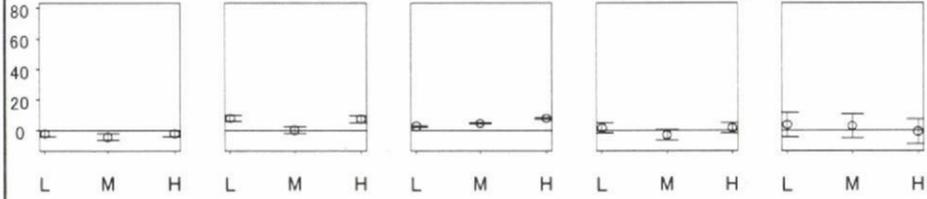


Fig. 6-SC

Table 6-SC

Chemical: C
Organ: Stomach Endpoint: PCT tail DNA
Transformation id Link: id

| Lab. | Variable | V - L | | | | V - M | | | | V - H | | | | J D | J L | | | |
|------|------------|--------|----|------|----------|----------|--------|----|------|----------|----------|--------|----|------|----------|----------|----------|-----|
| | | Effect | df | SE | Dunnnett | LSD | Effect | df | SE | Dunnnett | LSD | Effect | df | | | SE | Dunnnett | LSD |
| 1 | id(MEAN V) | -2.32 | 16 | 2.1 | 0.97 | 0.858 | -4.52 | 16 | 2.1 | 0.998 | 0.977 | -2.17 | 16 | 2.1 | 0.965 | 0.842 | 0 | 0 |
| 2 | id(MEAN V) | 7.9 | 16 | 2.27 | 0.004 | 0.002 | 0.11 | 16 | 2.27 | 0.732 | 0.48 | 7.43 | 16 | 2.27 | 0.006 | 0.002 | 1 | 1 |
| 3 | id(MEAN V) | 2.6 | 16 | 0.46 | 4.60E-05 | 1.60E-05 | 4.57 | 16 | 0.46 | 3.80E-08 | 1.30E-08 | 7.88 | 16 | 0.46 | 3.00E-11 | 4.00E-12 | 1 | 1 |
| 4 | id(MEAN V) | 1.58 | 16 | 3.33 | 0.555 | 0.32 | -3.07 | 16 | 3.33 | 0.955 | 0.815 | 1.52 | 16 | 3.33 | 0.564 | 0.327 | 0 | 0 |
| 5 | id(MEAN V) | 3.62 | 16 | 8.15 | 0.589 | 0.331 | 2.9 | 16 | 8.15 | 0.608 | 0.363 | -0.65 | 16 | 8.15 | 0.778 | 0.531 | 0 | 0 |

One side tests were performed

Endpoint: PCT Tail DNA Transformation: id Organ: Stomach

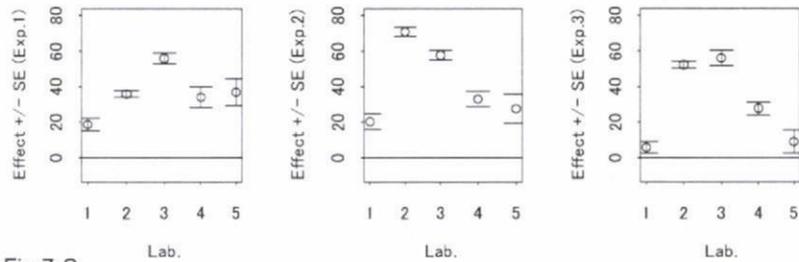


Fig 7-S

Table 7-S

Organ: Stomach Endpoint: PCT tail DNA
Transformation id Link: id

| Type | For Chem. | Variable | Lab | | | | | | | | | |
|-------|-----------|------------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|
| | | | 1 | | 2 | | 3 | | 4 | | 5 | |
| | | | Effect | Variance |
| INTRA | | | | 53.4757 | | 300.554 | | 0 | | 7.77E-07 | | 163.705 |
| EXP | A | id(MEAN V) | 18.581 | 13.1602 | 35.828 | 3.63801 | 55.78 | 9.15273 | 34.088 | 32.4868 | 36.903 | 58.3367 |
| | B | id(MEAN V) | 20.228 | 18.5957 | 70.809 | 6.90883 | 57.61 | 7.24577 | 32.951 | 18.5164 | 27.582 | 70.483 |
| | C | id(MEAN V) | 5.6343 | 9.69219 | 52.223 | 4.20841 | 55.924 | 17.5159 | 27.661 | 12.7567 | 8.8725 | 40.3883 |

Table 8-S

Organ: Stomach Endpoint: PCT tail DNA
Transformation: id Link: id

| Variable | Component | | Variance |
|------------|-------------|-----|----------|
| id(MEAN_V) | Chem.(Lab.) | | 103.05 |
| | Lab. | | 294.14 |
| | Residual | 1 A | 13.16 |
| | | 1 B | 18.596 |
| | | 1 C | 9.6922 |
| | | 2 A | 3.638 |
| | | 2 B | 6.9088 |
| | | 2 C | 4.2084 |
| | | 3 A | 9.1527 |
| | | 3 B | 7.2458 |
| | | 3 C | 17.516 |
| | | 4 A | 32.487 |
| | | 4 B | 18.516 |
| | | 4 C | 12.757 |
| | | 5 A | 58.337 |
| | | 5 B | 70.483 |
| | | 5 C | 40.388 |

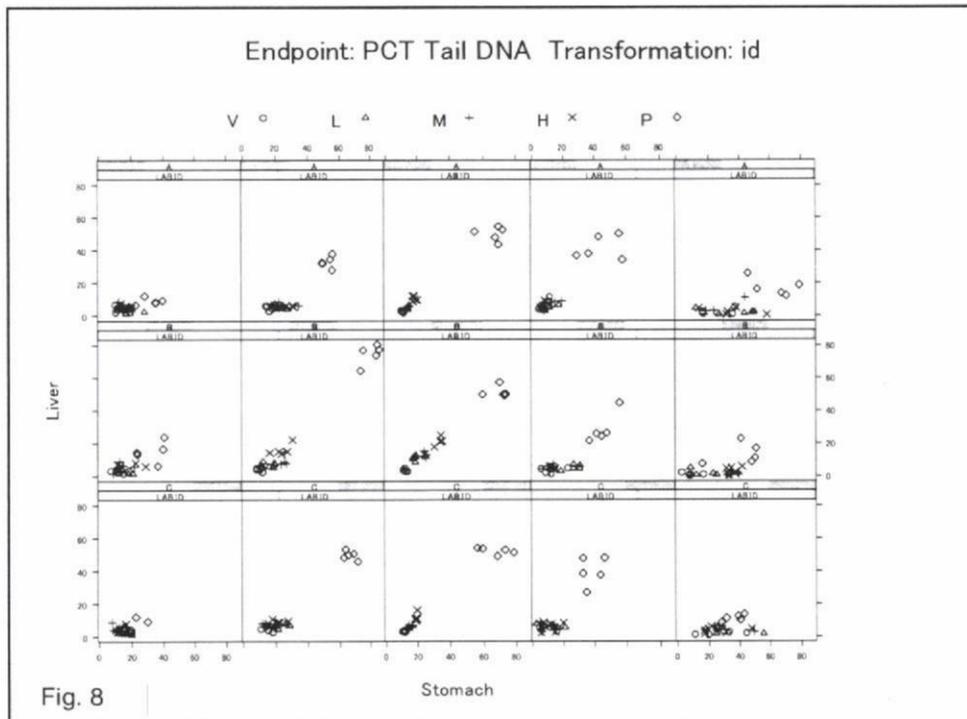
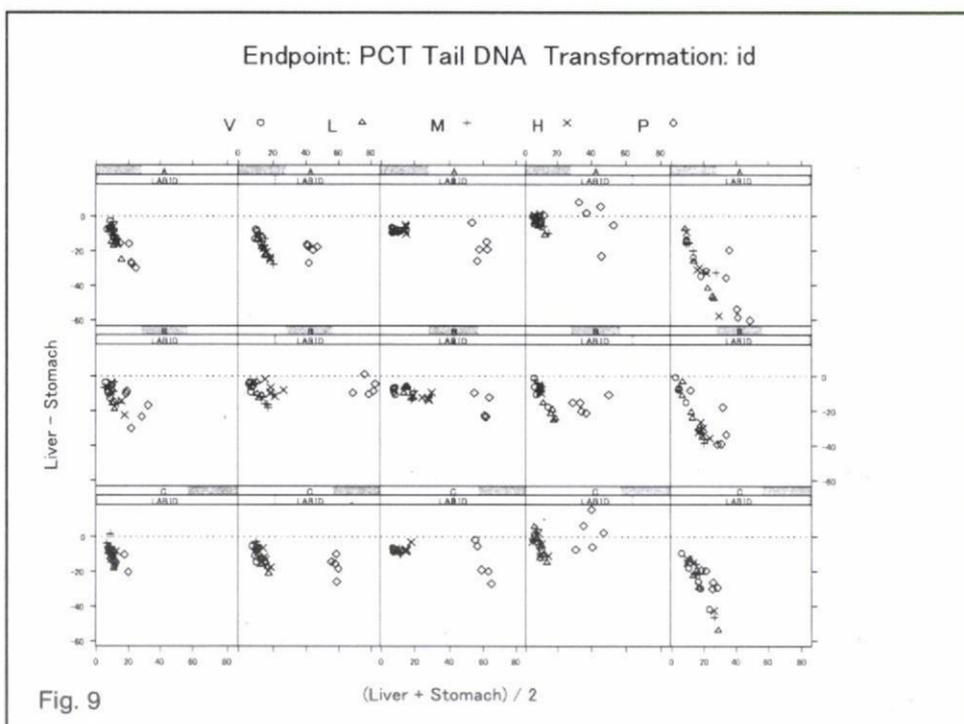


Table 9

Endpoint: PCT tail DNA
Transformation: id Link: id

| | | Lab. | | | | |
|----------|------------|------|------|------|------|------|
| | | 1 | 2 | 3 | 4 | 5 |
| Chemical | Variable | | | | | |
| A | id(MEAN V) | 0.46 | 0.91 | 0.98 | 0.92 | 0.58 |
| B | id(MEAN V) | 0.72 | 0.98 | 0.98 | 0.87 | 0.5 |
| C | id(MEAN V) | 0.3 | 0.97 | 0.98 | 0.88 | 0.24 |



INTERNATIONAL PRE-VALIDATION STUDY OF THE IN VITRO ALKALINE COMET ASSAY

Results

| | |
|------------------------------------|----|
| 1. Ethymethansulfonate (EMS) | 2 |
| 2. Mitomycin C (MMC) | 6 |
| 3. 2-Aminoanthracene (2AA) | 10 |
| 4. Cycloheximide (CHX) | 17 |
| 5. Triton X-100 (TRX) | 21 |

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1. Ethymethansulfonate (EMS)

Cytotoxicity Assays Results

TK6 cells after 4h Exposure to Ethymethansulfonate, without Metabolic Activation (-S9)

| Group No. | EMS Treatment (µg/mL) | Daily Cell Growth ^A Measured by COULTER COUNTER | | | Relative Suspension Growth (%) |
|-----------|-----------------------|---|-------|------------------|--------------------------------|
| | | Day 1 | Day 2 | Day 1 x Day 2 | |
| 1 | DMSO | 4.13 | 3.94 | 16.27 | 100.0 |
| 2 | 62.5 | 2.72 | 1.45 | 3.95 | 24.3 |
| 3 | 125 | 2.44 | 1.08 | 2.62 | 16.1 |
| 4 | 250 | 2.10 | 1.02 | 2.15 | 13.2 |
| 5 | 500 | 1.83 | 1.03 | 1.89 | 11.6 |
| 6 | 1000 | 1.46 | 1.01 | 1.47 | 9.1 |
| 7 | 2000 | 1.53 | 1.06 | 1.63 | 10.0 |

^A Cell conc. on the day / Cell conc. on the day before

Day 1: After 24h from end of treatment

Day 2: After 48h from end of treatment

| Group No. | EMS Treatment (µg/mL) | % Viability ^B Measured by Dye Exclusion Assay | | |
|-----------|-----------------------|---|-------|-------|
| | | Day 0 | Day 1 | Day 2 |
| 1 | DMSO | 97.5 | 97.8 | 100.0 |
| 2 | 62.5 | 100.0 | 97.1 | 91.7 |
| 3 | 125 | 100.0 | 100.0 | 40.6 |
| 4 | 250 | 96.9 | 98.1 | 50.0 |
| 5 | 500 | 97.3 | 79.5 | 18.8 |
| 6 | 1000 | 97.4 | 46.5 | 6.9 |
| 7 | 2000 | 96.7 | 23.5 | 0.0 |

^B Number of unstained cells / number of total cells) x 100

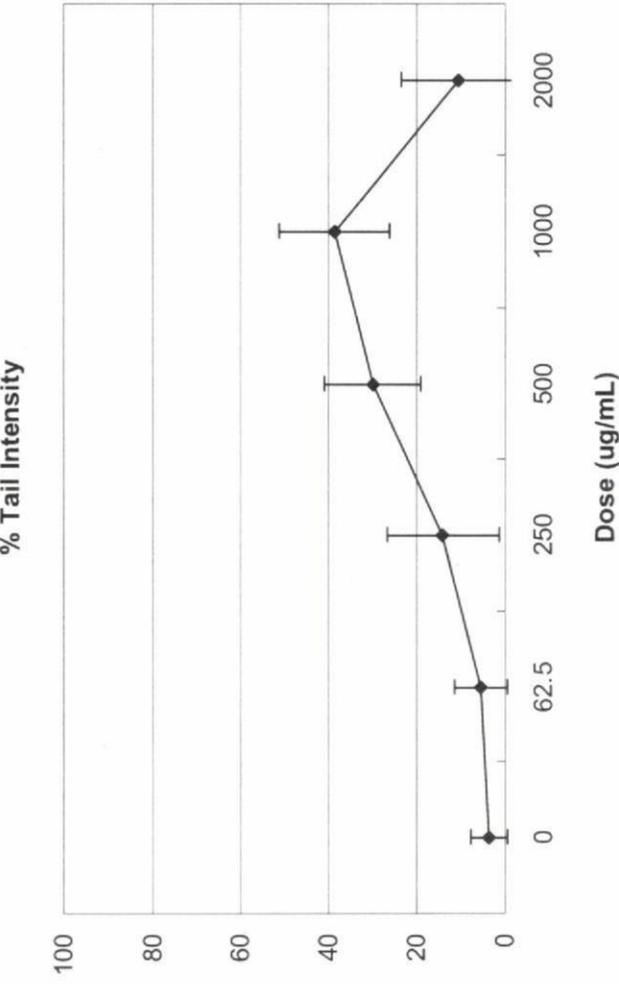
Day 0: Just after treatment

Day 1: After 24h from end of treatment

Day 2: After 48h from end of treatment

Comet Assay Results

TK6 cells after 4h Exposure to Ethymethansulfonate, without Metabolic Activation (-S9)



2000 µg/mL EMS
Hedgehog (small head)

| Group No. | EMS Treatment (µg/mL) | Analyzed Cell No. | Data ^A from Comet Assay IV | | |
|-----------|-----------------------|-------------------|---------------------------------------|-------------|------------------|
| | | | Tail Moment | Tail Length | % Tail Intensity |
| 1 | DMSO | 100 | 0.72 | 43.05 | 3.47 |
| 2 | 62.5 | 100 | 1.18 | 49.00 | 5.52 |
| - | 125 | -* | - | - | - |
| 3 | 250 | 100 | 3.21 | 56.45 | 14.01 |
| 4 | 500 | 100 | 8.32 | 75.24 | 30.19 |
| 5 | 1000 | 100 | 11.91 | 81.45 | 38.98 |
| 6 | 2000 | 100 | 3.41 | 74.04 | 10.37 |

^A Mean of analyzed cells

* Not scored due to drop of agarose gel on slide

In vitro Micronucleus Assay Results

**TK6 cells after 4h Exposure to Ethymethansulfonate,
without Metabolic Activation (-S9)**

| Group No. | EMS Treatment (µg/mL) | Analyzed Cell No. | Number of Micronucleated cell (% Incidence) |
|-----------|-----------------------|-------------------|---|
| 1 | DMSO | 1000 | 4 (0.4) |
| 2 | 62.5 | 1000 | 68 (6.8) |
| 3 | 125 | 1000 | 74 (7.4) |
| 4 | 250 | 1000 | 84 (8.4) |
| 5 | 500 | 720 | 49 (6.8) |
| 6 | 1000 | TOX | - (-) |
| 7 | 2000 | TOX | - (-) |

TOX: Not scored due to cytotoxicity

Micronucleus assay was performed on Day 2.

2. Mitomycin C (MMC)

Cytotoxicity Assays Results

TK6 cells after 4h Exposure to Mitomycin C, without Metabolic Activation (-S9)

| Group No. | MMC Treatment (µg/mL) | Daily Cell Growth ^A Measured by COULTER COUNTER | | | Relative Suspension Growth (%) |
|-----------|-----------------------|---|-------|------------------|--------------------------------|
| | | Day 1 | Day 2 | Day 1 x Day 2 | |
| 1 | Saline | 3.72 | 3.82 | 14.20 | 100.0 |
| 2 | 0.125 | 2.18 | 2.54 | 5.54 | 39.0 |
| 3 | 0.25 | 1.43 | 1.61 | 2.32 | 16.3 |
| 4 | 0.5 | 1.16 | 1.29 | 1.50 | 10.6 |
| 5 | 1 | 1.00 | 0.93 | 0.93 | 6.6 |
| 6 | 2 | 0.89 | 0.88 | 0.78 | 5.5 |
| 7 | 4 | 0.87 | 0.95 | 0.83 | 5.8 |

^A Cell conc. on the day / Cell conc. on the day before

Day 1: After 24h from end of treatment

Day 2: After 48h from end of treatment

| Group No. | MMC Treatment (µg/mL) | % Viability ^B Measured by Dye Exclusion Assay | | |
|-----------|-----------------------|---|-------|-------|
| | | Day 0 | Day 1 | Day 2 |
| 1 | Saline | 97.0 | 98.0 | 100.0 |
| 2 | 0.125 | 100.0 | 95.6 | 84.4 |
| 3 | 0.25 | 100.0 | 91.5 | 67.2 |
| 4 | 0.5 | 97.3 | 78.1 | 34.4 |
| 5 | 1 | 100.0 | 53.8 | 6.1 |
| 6 | 2 | 100.0 | 35.7 | 15.0 |
| 7 | 4 | 97.1 | 31.4 | 0.0 |

^B Number of unstained cells / number of total cells) x 100

Day 0: Just after treatment

Day 1: After 24h from end of treatment

Day 2: After 48h from end of treatment

Comet Assay Results

TK6 cells after 4h Exposure to Mitomycin C, without Metabolic Activation (-S9)

| Group No. | MMC Treatment (µg/mL) | Analyzed Cell No. | Data ^A from Comet Assay IV | | |
|-----------|-----------------------|-------------------|---------------------------------------|-------------|------------------|
| | | | Tail Moment | Tail Length | % Tail Intensity |
| 1 | Saline | 100 | 1.48 | 46.42 | 5.48 |
| 2 | 0.125 | 100 | 0.54 | 44.61 | 2.20 |
| 3 | 0.25 | 100 | 0.93 | 42.20 | 4.61 |
| 4 | 0.5 | 100 | 0.66 | 42.39 | 2.62 |
| 5 | 1 | 100 | 0.73 | 42.71 | 2.71 |
| 6 | 2 | 100 | 0.54 | 44.01 | 2.26 |
| 7 | 4 | 100 | 0.55 | 45.77 | 3.03 |

^A Mean of analyzed cells

