

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Appendix 13 Offspring Reflexological Responses - Individual Values

DOSE LEVEL: 0 (Control)

| Litter Number | Surface Righting Reflex | | |
|------------------|---------------------------------|-------------------------------|-------------|
| | Number of Offspring Examined | Number of Offspring Passed | % Passed |
| 11 | 12 | 9 | 75.0 |
| 12 | 14 | 14 | 100.0 |
| 13 | 14 | 10 | 71.4 |
| 14 | 13 | 8 | 61.5 |
| 15 TLL | - | - | - |
| 16 | 15 | 10 | 66.7 |
| 17FD | - | - | - |
| 18 | 17 | 15 | 88.2 |
| 19 | 14 | 9 | 64.3 |
| 20 | 16 | 11 | 68.8 |

TLL = total litter loss
FD = found dead
- = not applicable

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 13 (continued) Offspring Reflexological Responses - Individual Values**

DOSE LEVEL: 50 mg/kg/day

| Litter Number | Surface Righting Reflex | | |
|---------------|------------------------------|----------------------------|----------|
| | Number of Offspring Examined | Number of Offspring Passed | % Passed |
| 31 | 12 | 12 | 100.0 |
| 32 | 18 | 11 | 61.1 |
| 33 | 14 | 11 | 78.6 |
| 34 | 14 | 13 | 92.9 |
| 35 | 13 | 13 | 100.0 |
| 36 | 12 | 10 | 83.3 |
| 37 | 3 | 3 | 100.0 |
| 38 | 13 | 11 | 84.6 |
| 39 | 15 | 12 | 80.0 |
| 40 | 15 | 15 | 100.0 |

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Appendix 13 (continued) Offspring Reflexological Responses - Individual Values

DOSE LEVEL: 150 mg/kg/day

| Litter Number | Surface Righting Reflex | | |
|---------------|------------------------------|----------------------------|----------|
| | Number of Offspring Examined | Number of Offspring Passed | % Passed |
| 51 | 14 | 13 | 92.9 |
| 52 | 16 | 15 | 93.8 |
| 53 | 6 | 5 | 83.3 |
| 54 | 14 | 13 | 92.9 |
| 55 | 14 | 11 | 78.6 |
| 56 | 15 | 15 | 100.0 |
| 57 | 14 | 14 | 100.0 |
| 58 | 12 | 12 | 100.0 |
| 59 | 13† | 11 | 84.6 |
| 60 | 9 | 9 | 100.0 |

† = one offspring not assessed in error

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Appendix 13 (continued) Offspring Reflexological Responses - Individual Values

DOSE LEVEL: 500 mg/kg/day

| Litter Number | Surface Righting Reflex | | |
|---------------|------------------------------|----------------------------|----------|
| | Number of Offspring Examined | Number of Offspring Passed | % Passed |
| 71 TLL | - | - | - |
| 72 NYB | - | - | - |
| 73 | 4 | 2 | 50.0 |
| 74 | 9 | 8 | 88.9 |
| 75 NP | - | - | - |
| 76 | 4 | 3 | 75.0 |
| 77 FTM | - | - | - |
| 78 | 14 | 14 | 100.0 |
| 79 | 6 | 6 | 100.0 |
| 80 | 4 | 4 | 100.0 |

TLL = total litter loss

NYB = implantation detected in uterus but no offspring observed to be born

NP = not pregnant

FTM = failed to mate

- = not applicable

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 14 Necropsy Findings of Offspring - Individual Observations

DOSE LEVEL: 0 (Control)

| Litter Number | Necropsy Day (Post Partum): | Interim Deaths | | Terminal kill Day 5 Post Partum | |
|---------------|--------------------------------|---------------------|--|--------------------------------------|--|
| | | Offspring Number | Macroscopic Observation | Offspring Number | Macroscopic Observation |
| 11 | - | - | - | Whole litter (3♂, 9♀) | No abnormalities detected |
| 12 | - | - | - | Whole litter (8♂, 6♀) | No abnormalities detected |
| 13 | - | - | - | Remaining litter (11♂, 2♀) F13 | Bruised, swollen left eye No abnormalities detected |
| 14 | - | - | - | Whole litter (5♂, 8♀) | No abnormalities detected |
| 15 TLL | Pre-Day 1 | * | One male, one female and one offspring of undetermined sex cannibalised, one male and four females autolysed, two males and two females no abnormalities detected. All offspring still in amniotic sacs. | - | - |
| 16 | - | - | - | Whole litter (12♂, 3♀) | No abnormalities detected |
| 17 FD | Pre-Day 1 1 | * | One female no abnormalities detected Six males and seven females killed due to death of dam - no abnormalities detected. | - | - |
| 18 | Pre-Day 1 | * | One male, no abnormalities detected | Whole litter (6♂, 11♀) | No abnormalities detected |
| 19 | - | - | - | Whole litter (9♂, 5♀) | No abnormalities detected |
| 20 | - | - | - | Whole litter (8♂, 8♀) | No abnormalities detected |

♂ = male
♀ = female

TLL = total litter loss
FD = found dead

- = not applicable

* = prior to allocation of within litter identity

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 14 (continued) Necropsy Findings of Offspring – Individual Observations

DOSE LEVEL: 50 mg/kg/day

| Litter Number | Interim Deaths | | | Terminal kill Day 5 <i>Post Partum</i> | |
|---------------|---|---------------------|---|---|---------------------------|
| | Necropsy Day (<i>Post Partum</i>): | Offspring Number | Macroscopic Observation | Offspring Number | Macroscopic Observation |
| 31 | - | - | - | Whole litter (5♂, 7♀) | No abnormalities detected |
| 32 | 5 | F18 | No abnormalities detected | Whole litter (10♂, 7♀) | No abnormalities detected |
| 33 | Pre-Day 1 | * | One female, autolysed | Whole litter (6♂, 8♀) | No abnormalities detected |
| 34 | - | - | - | Whole litter (9♂, 5♀) | No abnormalities detected |
| 35 | - | - | - | Whole litter (5♂, 7♀) | No abnormalities detected |
| 36 | Pre-Day 1 | * | One male and one female, no abnormalities detected | Whole litter (6♂, 6♀) | No abnormalities detected |
| 37 | Pre-Day 1 | * | One male and one female autolysed | Whole litter (2♂, 1♀) | No abnormalities detected |
| 38 | - | - | - | Whole litter (6♂, 7♀) | No abnormalities detected |
| 39 | Pre-Day 1 | * | One female, autolysed | Whole litter (7♂, 8♀) | No abnormalities detected |
| 40 | - | - | - | Whole litter (7♂, 8♀) | No abnormalities detected |

♂ = male
 ♀ = female
 F = female
 - = not applicable
 * = prior to allocation of within litter identity

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 14 (continued) Necropsy Findings of Offspring – Individual Observations

DOSE LEVEL: 150 mg/kg/day

| Litter Number | Necropsy Day (<i>Post Partum</i>); | Interim Deaths | | Macroscopic Observation | Offspring Number | Terminal kill Day 5 <i>Post Partum</i> | Macroscopic Observation |
|---------------|--------------------------------------|------------------|-------------------------------------|-------------------------------------|-------------------------------------|---|---|
| | | Offspring Number | Macroscopic Observation | | | | |
| 51 | - | - | - | - | Whole litter (12♂, 2♀) | | No abnormalities detected |
| 52 | - | - | - | - | Whole litter (12♂, 4♀) | | No abnormalities detected |
| 53 | - | - | - | - | Whole litter (2♂, 4♀) | | No abnormalities detected |
| 54 | 5 | F8 | No abnormalities detected | No abnormalities detected | Whole litter (3♂, 1♀) | | No abnormalities detected |
| 55 | - | - | - | - | Whole litter (7♂, 7♀) | | No abnormalities detected |
| 56 | 3 | M4 | Autolysed | Autolysed | Whole litter (3♂, 11♀) | | No abnormalities detected |
| 57 | - | - | - | - | Whole litter (7♂, 7♀) | | No abnormalities detected |
| 58 | 1 | * | One female autolysed | One female autolysed | F10 Remaining litter (4♂, 7♀) | | No abnormalities detected Small, swollen right hindlimb No abnormalities detected |
| 59 | Pre-Day 1 | * | One male, no abnormalities detected | One male, no abnormalities detected | Whole litter (5♂, 9♀) | | No abnormalities detected |
| 60 | - | - | - | - | Whole litter (4♂, 5♀) | | No abnormalities detected |

♂ = male
 ♀ = female
 M = male
 F = female
 - = not applicable
 * = prior to allocation of within litter identity

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 14 (continued) Necropsy Findings of Offspring – Individual Observations

DOSE LEVEL: 500 mg/kg/day

| Litter Number | Interim Deaths | | | Terminal kill Day 5 Post Partum | |
|---------------|--------------------------------------|---------------------|---|------------------------------------|------------------------------------|
| | Necropsy Day <i>Post Partum</i> : | Offspring Number | Macroscopic Observation | Offspring Number | Macroscopic Observation |
| 71 TLL | Pre-Day 1 1 | * * | One female, autolysed One male, no milk in stomach | - | - |
| 72 NYB | - | - | - | - | - |
| 73 | - | - | - | Whole litter (1♂, 3♀) | No abnormalities detected |
| 74 | - | - | - | Whole litter (4♂, 5♀) | No abnormalities detected |
| 75 NP | - | - | - | - | - |
| 76 | - | - | - | Whole litter (2♂, 2♀) | No abnormalities detected |
| 77 FTM | - | - | - | - | - |
| 78 | - | - | - | Whole litter (7♂, 7♀) | No abnormalities detected |
| 79 | - | - | - | F5 Remaining litter (2♂, 3♀) | Small No abnormalities detected |
| 80 | - | - | - | Whole litter (4♂) | No abnormalities detected |

♂ = male
 ♀ = female
 F = female
 TLL = total litter loss
 NP = not pregnant
 FTM = failed to mate
 NYB = implantation detected in uterus but no offspring observed to be born
 - = not applicable
 * = prior to allocation of within litter identity

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT****Appendix 15 Necropsy Findings of Males – Individual Observations**

DOSE LEVEL: 0 (Control)

| Animal Number | Day of Necropsy | Macroscopic Observations |
|---------------|-----------------|---------------------------|
| 1 | 43 | No abnormalities detected |
| 2 | 43 | No abnormalities detected |
| 3 | 43 | No abnormalities detected |
| 4 | 43 | No abnormalities detected |
| 5 | 43 | No abnormalities detected |
| 6 | 43 | No abnormalities detected |
| 7 | 43 | No abnormalities detected |
| 8 | 43 | No abnormalities detected |
| 9 | 43 | No abnormalities detected |
| 10 | 43 | No abnormalities detected |

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 15 (continued) Necropsy Findings of Males – Individual Observations**

DOSE LEVEL: 50 mg/kg/day

| Animal Number | Day of Necropsy | Macroscopic Observations |
|---------------|-----------------|---------------------------|
| 21 | 43 | No abnormalities detected |
| 22 | 43 | No abnormalities detected |
| 23 | 43 | No abnormalities detected |
| 24 | 43 | No abnormalities detected |
| 25 | 43 | No abnormalities detected |
| 26 | 43 | No abnormalities detected |
| 27 | 43 | No abnormalities detected |
| 28 | 43 | No abnormalities detected |
| 29 | 43 | No abnormalities detected |
| 30 | 43 | No abnormalities detected |

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 15 (continued) Necropsy Findings of Males – Individual Observations**

DOSE LEVEL: 150 mg/kg/day

| Animal Number | Day of Necropsy | Macroscopic Observations |
|---------------|-----------------|---|
| 41 | 43 | No abnormalities detected |
| 42 | 43 | No abnormalities detected |
| 43 | 43 | Kidneys: left - small, right - enlarged, increased renal pelvic capacity |
| 44 | 43 | No abnormalities detected |
| 45 | 43 | No abnormalities detected |
| 46 | 43 | No abnormalities detected |
| 47 | 43 | No abnormalities detected |
| 48 | 43 | No abnormalities detected |
| 49+ | 43 | No abnormalities detected |
| 50 | 43 | No abnormalities detected |

+ = animal killed by cervical dislocation due to difficulties with intravenous euthanasia

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Appendix 15 (continued) Necropsy Findings of Males – Individual Observations

DOSE LEVEL: 500 mg/kg/day

| Animal Number | Day of Necropsy | Macroscopic Observations |
|---------------|-----------------|--|
| 61 | 43 | No abnormalities detected |
| 62 | 43 | <i>Staining of the fur</i> |
| 63 | 43 | No abnormalities detected |
| 64 | 43 | <i>Staining of the fur</i> |
| 65• | 43 | No abnormalities detected |
| 66 | 43 | No abnormalities detected |
| 67 FTM | 43 | No abnormalities detected |
| 68 | 43 | <i>Staining of the fur</i> |
| 69 | 43 | <i>Staining of the fur</i> <i>Stained snout</i> |
| 70 KIE | 2 | Thymus: enlarged Lungs: Right - cranial, intermediate and caudal lobes encased in white fibrous tissue Thoracic cavity: filled with red fluid |

External observations are presented in italics

• = failed to induce pregnancy in female partner

FTM = failed to mate

KIE = killed *in extremis*

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Appendix 16 Necropsy Findings of Females – Individual Observations

DOSE LEVEL: 0 (Control)

| Animal Number | Day of Necropsy | Macroscopic Observations |
|---------------|-----------------|---|
| 11 | 46 | No abnormalities detected |
| 12 | 45 | No abnormalities detected |
| 13 | 46 | No abnormalities detected |
| 14 | 44 | No abnormalities detected |
| 15 TLL | 43 | Ovary right: encased in a fluid filled sac |
| 16 | 45 | No abnormalities detected |
| 17 FD | 41 | <i>Red staining around ano genital region</i> Lungs: reddened Liver: dark Gastro-intestinal tract: gaseous distension Uterus dark |
| 18 | 44 | No abnormalities detected |
| 19 | 43 | <i>Generalised fur loss</i> |
| 20 | 45 | No abnormalities detected |

External observations are presented in italics

TLL = total litter loss

FD = found dead

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 16 (continued) Necropsy Findings of Females – Individual Observations**

DOSE LEVEL: 50 mg/kg/day

| Animal Number | Day of Necropsy | Macroscopic Observations |
|---------------|-----------------|---------------------------|
| 31 | 45 | No abnormalities detected |
| 32 | 44 | No abnormalities detected |
| 33 | 45 | No abnormalities detected |
| 34 | 45 | No abnormalities detected |
| 35 | 43 | No abnormalities detected |
| 36 | 46 | No abnormalities detected |
| 37 | 45 | Lungs: reddened |
| 38 | 49 | No abnormalities detected |
| 39 | 43 | No abnormalities detected |
| 40 | 46 | No abnormalities detected |

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 16 (continued) Necropsy Findings of Females – Individual Observations****DOSE LEVEL:** 150 mg/kg/day

| Animal Number | Day of Necropsy | Macroscopic Observations |
|---------------|-----------------|---------------------------|
| 51 | 46 | No abnormalities detected |
| 52 | 46 | No abnormalities detected |
| 53U | 46 | No abnormalities detected |
| 54 | 45 | No abnormalities detected |
| 55 | 46 | No abnormalities detected |
| 56 | 44 | No abnormalities detected |
| 57 | 44 | No abnormalities detected |
| 58 | 43 | No abnormalities detected |
| 59 | 46 | No abnormalities detected |
| 60 | 43 | No abnormalities detected |

U = unilateral implantation

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Appendix 16 (continued) Necropsy Findings of Females – Individual Observations

DOSE LEVEL: 500 mg/kg/day

| Animal Number | Day of Necropsy | Macroscopic Observations |
|---------------|-----------------|----------------------------|
| 71 TLL | 57 | No abnormalities detected |
| 72 NYB | 48 | No abnormalities detected |
| 73 | 44 | No abnormalities detected |
| 74 | 49 | No abnormalities detected |
| 75 NP | 43 | No abnormalities detected |
| 76 | 48 | No abnormalities detected |
| 77 FTM | 43 | <i>Staining of the fur</i> |
| 78 | 45 | No abnormalities detected |
| 79 | 50 | No abnormalities detected |
| 80 | 47 | No abnormalities detected |

External observations are presented in italics

TLL = total litter loss

NYB = implantation detected in uterus but no offspring observed to be born

NP = not pregnant

FTM = failed to mate

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

**Appendix 17 Absolute and Bodyweight-Relative Male Reproductive Organ Weights –
Individual Values**

DOSE LEVEL: 0 (Control)

| Animal Number | Day of Necropsy | Bodyweight (g) at Terminal Kill | Organ Weight (g) | |
|---------------|-----------------|---------------------------------|------------------|--------|
| | | | Epididymides | Testes |
| 1 | 43 | 452 | 1.3632 | 3.4193 |
| 2 | 43 | 514 | 1.5360 | 4.0459 |
| 3 | 43 | 453 | 1.2656 | 3.6903 |
| 4 | 43 | 411 | 1.2138 | 3.4618 |
| 5 | 43 | 486 | 1.4037 | 3.6932 |
| 6 | 43 | 472 | 1.5445 | 3.7020 |
| 7 | 43 | 461 | 1.1685 | 3.5607 |
| 8 | 43 | 429 | 1.4012 | 3.7737 |
| 9 | 43 | 384 | 1.1921 | 3.2226 |
| 10 | 43 | 450 | 1.4956 | 3.5772 |

| Animal Number | Day of Necropsy | Bodyweight (g) at Terminal Kill | Relative Organ Weight (%) | |
|---------------|-----------------|---------------------------------|---------------------------|--------|
| | | | Epididymides | Testes |
| 1 | 43 | 452 | 0.3016 | 0.7565 |
| 2 | 43 | 514 | 0.2988 | 0.7871 |
| 3 | 43 | 453 | 0.2794 | 0.8146 |
| 4 | 43 | 411 | 0.2953 | 0.8423 |
| 5 | 43 | 486 | 0.2888 | 0.7599 |
| 6 | 43 | 472 | 0.3272 | 0.7843 |
| 7 | 43 | 461 | 0.2535 | 0.7724 |
| 8 | 43 | 429 | 0.3266 | 0.8797 |
| 9 | 43 | 384 | 0.3104 | 0.8392 |
| 10 | 43 | 450 | 0.3324 | 0.7949 |

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

**Appendix 17 (continued) Absolute and Bodyweight-Relative Male Reproductive Organ
Weights – Individual Values**

DOSE LEVEL: 50 mg/kg/day

| Animal Number | Day of Necropsy | Bodyweight (g) at Terminal Kill | Organ Weight (g) | |
|---------------|-----------------|---------------------------------|------------------|--------|
| | | | Epididymides | Testes |
| 21 | 43 | 464 | 1.2844 | 3.1782 |
| 22 | 43 | 513 | 1.3497 | 3.4381 |
| 23 | 43 | 475 | 1.1876 | 3.6243 |
| 24 | 43 | 482 | 1.2486 | 3.0676 |
| 25 | 43 | 414 | 1.2365 | 2.9578 |
| 26 | 43 | 505 | 1.4901 | 3.4459 |
| 27 | 43 | 388 | 1.1047 | 3.9263 |
| 28 | 43 | 483 | 1.4208 | 3.7947 |
| 29 | 43 | 443 | 1.1380 | 3.5077 |
| 30 | 43 | 423 | 1.2846 | 3.1553 |

| Animal Number | Day of Necropsy | Bodyweight (g) at Terminal Kill | Relative Organ Weight (%) | |
|---------------|-----------------|---------------------------------|---------------------------|--------|
| | | | Epididymides | Testes |
| 21 | 43 | 464 | 0.2768 | 0.6850 |
| 22 | 43 | 513 | 0.2631 | 0.6702 |
| 23 | 43 | 475 | 0.2500 | 0.7630 |
| 24 | 43 | 482 | 0.2590 | 0.6364 |
| 25 | 43 | 414 | 0.2987 | 0.7144 |
| 26 | 43 | 505 | 0.2951 | 0.6824 |
| 27 | 43 | 388 | 0.2847 | 1.0119 |
| 28 | 43 | 483 | 0.2942 | 0.7857 |
| 29 | 43 | 443 | 0.2569 | 0.7918 |
| 30 | 43 | 423 | 0.3037 | 0.7459 |

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

**Appendix 17 (continued) Absolute and Bodyweight-Relative Male Reproductive Organ
Weights – Individual Values**

DOSE LEVEL: 150 mg/kg/day

| Animal Number | Day of Necropsy | Bodyweight (g) at Terminal Kill | Organ Weight (g) | |
|---------------|-----------------|---------------------------------|------------------|--------|
| | | | Epididymides | Testes |
| 41 | 43 | 437 | 1.1697 | 2.7901 |
| 42 | 43 | 464 | 1.2882 | 3.1052 |
| 43 | 43 | 476 | 1.3656 | 3.4112 |
| 44 | 43 | 505 | 1.2147 | 3.2573 |
| 45 | 43 | 466 | 1.3752 | 3.7280 |
| 46 | 43 | 432 | 1.2218 | 3.1547 |
| 47 | 43 | 478 | 1.1707 | 2.9650 |
| 48 | 43 | 418 | 1.2845 | 3.1814 |
| 49 | 43 | 494 | 1.4193 | 3.7101 |
| 50 | 43 | 440 | 1.2074 | 3.2975 |

| Animal Number | Day of Necropsy | Bodyweight (g) at Terminal Kill | Relative Organ Weight (%) | |
|---------------|-----------------|---------------------------------|---------------------------|--------|
| | | | Epididymides | Testes |
| 41 | 43 | 437 | 0.2677 | 0.6385 |
| 42 | 43 | 464 | 0.2776 | 0.6692 |
| 43 | 43 | 476 | 0.2869 | 0.7166 |
| 44 | 43 | 505 | 0.2405 | 0.6450 |
| 45 | 43 | 466 | 0.2951 | 0.8000 |
| 46 | 43 | 432 | 0.2828 | 0.7303 |
| 47 | 43 | 478 | 0.2449 | 0.6203 |
| 48 | 43 | 418 | 0.3073 | 0.7611 |
| 49 | 43 | 494 | 0.2873 | 0.7510 |
| 50 | 43 | 440 | 0.2744 | 0.7494 |

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

**Appendix 17 (continued) Absolute and Bodyweight-Relative Male Reproductive Organ
Weights – Individual Values**

DOSE LEVEL: 500 mg/kg/day

| Animal Number | Day of Necropsy | Bodyweight (g) at Terminal Kill | Organ Weight (g) | |
|---------------|-----------------|---------------------------------|------------------|--------|
| | | | Epididymides | Testes |
| 61 | 43 | 411 | 0.9867 | 3.0055 |
| 62 | 43 | 481 | 1.2413 | 3.3098 |
| 63 | 43 | 409 | 1.0985 | 3.4448 |
| 64 | 43 | 516 | 1.0893 | 3.2545 |
| 65 • | 43 | 470 | 1.0161 | 2.8126 |
| 66 | 43 | 352 | 0.9625 | 3.1063 |
| 67 FTM | 43 | 423 | 1.1377 | 3.1745 |
| 68 | 43 | 448 | 1.0191 | 3.2064 |
| 69 | 43 | 492 | 1.0639 | 3.3425 |
| 70 KIE | 2 | - | - | - |

| Animal Number | Day of Necropsy | Bodyweight (g) at Terminal Kill | Relative Organ Weight (%) | |
|---------------|-----------------|---------------------------------|---------------------------|--------|
| | | | Epididymides | Testes |
| 61 | 43 | 411 | 0.2401 | 0.7313 |
| 62 | 43 | 481 | 0.2581 | 0.6881 |
| 63 | 43 | 409 | 0.2686 | 0.8422 |
| 64 | 43 | 516 | 0.2111 | 0.6307 |
| 65 • | 43 | 470 | 0.2162 | 0.5984 |
| 66 | 43 | 352 | 0.2734 | 0.8825 |
| 67 FTM | 43 | 423 | 0.2690 | 0.7505 |
| 68 | 43 | 448 | 0.2275 | 0.7157 |
| 69 | 43 | 492 | 0.2162 | 0.6794 |
| 70 KIE | 2 | - | - | - |

• = failed to induce pregnancy in female partner

FTM = failed to mate

KIE = killed *in extremis*

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Appendix 18 Histopathological Findings for Males – Individual Observations

DOSE LEVEL: 0 (Control)

| Animal Number and Sex | Mode of Death | Tissue | Observation |
|-----------------------|---------------|---------------------------------|---|
| 1 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 2 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (slight) |
| 3 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 4 M | Terminal kill | Coagulating glands Pituitary | One section examined Vacuolation pars anterior cells (minimal) |
| 5 M | Terminal kill | Coagulating glands Pituitary | one section examined Vacuolation pars anterior cells (minimal) |
| 6 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 7 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 8 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (slight) |
| 9 M | Terminal kill | Coagulating glands Pituitary | one section examined Vacuolation pars anterior cells (slight) |
| 10 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (slight) |

M = male

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Appendix 18 (continued) Histopathological Findings for Males – Individual Observations

DOSE LEVEL: 500 mg/kg/day

| Animal Number and Sex | Mode of Death | Tissue | Observation |
|-----------------------|---------------|-----------|--|
| 61 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (slight) |
| 62 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 63 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 64 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 65 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 66 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 67 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (slight) |
| 68 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 69 M | Terminal kill | Pituitary | Vacuolation pars anterior cells (minimal) |
| 70 M | Interim death | Pituitary | Vacuolation pars anterior cells (minimal) |
| | | Lungs | Pleuritis and peripheral acute inflammatory cell infiltrates |
| | | Thymus | No evidence gross lesion |

M = male

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 Histopathological Findings for Females – Individual Observations

DOSE LEVEL: 0 (Control)

| Animal Number and Sex | Mode of Death | Tissue | Observation |
|-----------------------|---------------|--|---|
| 11 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 12 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 13 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 14 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 15 F | Terminal kill | Uterus/cervix Vagina | Keratinisation cervix Peripheral foam cells/haemorrhage/pigment Epithelial keratinisation |
| 16 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 17 F | Interim death | Pituitary Uterus/cervix Vagina Intestinal tract Liver Lungs | No tissue available Congestion Epithelial keratinisation Autolysis (moderate) Congestion Peribronchiolar lymphoid aggregations (minimal) Congestion |
| 18 F | Terminal kill | Uterus/cervix Vagina | Peripheral foam cells/haemorrhage/pigment No tissue available |
| 19 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 20 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |

F = female

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Histopathological Findings for Females – Individual Observations

DOSE LEVEL: 500 mg/kg/day

| Animal Number and Sex | Mode of Death | Tissue | Observation |
|-----------------------|---------------|-----------------------------|--|
| 71 F | Terminal kill | Uterus/cervix Vagina | Keratinisation cervix Peripheral foam cells/haemorrhage/pigment Epithelial keratinisation |
| 72 F | Terminal kill | | No abnormality detected |
| 73 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 74 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 75 F | Terminal kill | | No abnormality detected |
| 76 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 77 F | Terminal kill | Uterus/cervix Vagina | Dilatation horn1 (slight) Dilatation horn2 (slight) Keratinisation cervix Epithelial keratinisation |
| 78 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 79 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |
| 80 F | Terminal kill | Uterus/cervix | Peripheral foam cells/haemorrhage/pigment |

F = female

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 20 Chemical Analysis of Test Material Formulations, Methods and Results****1. METHOD OF ANALYSIS****1.1 Summary**

The concentration of Dibromomethane in the test material formulations was determined by gas chromatography (GC) using an external standard technique.

1.2 Samples

The test material formulations were diluted with acetone to give a final, theoretical test material concentration of approximately 0.1 mg/ml.

1.3 Standards

Standard solutions of test material were prepared in acetone at a nominal concentration of 0.1 mg/ml.

1.4 Procedure

The standard and sample solutions were analysed by GC using the following conditions:

| | | |
|---------------------------------------|---|--|
| GC system | : | Agilent Technologies 5890, incorporating autosampler and workstation |
| Column | : | DB-5 (30 m x 0.53 mm id x 5 µm film) |
| Oven temperature program | : | initial 50 °C for 2 mins rate 10 °C/min temp 130 °C for 0 mins rate 50°C/min final 300 °C for 5 mins |
| Injection temperature | : | 300°C |
| Flame ionisation detector temperature | : | 300°C |
| Injection volume | : | 1 µl |
| Retention time | : | ~ 5.7 mins |

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

1.5 Homogeneity Determinations

The test material formulations were mixed thoroughly and samples were taken from the top, middle and bottom of the container, shaking between sampling. Sampling was performed in triplicate.

1.6 Stability Determinations

The test material formulations were sampled and analysed initially and then after storage at approximately +4°C in the dark for fourteen days.

1.7 Verification of Test Material Formulation Concentrations

The test material formulations were sampled and analysed within three days of preparation.

2. RESULTS

2.1 Homogeneity of Test Material Formulations

| Nominal Concentration (mg/ml) | Sampling Location | Concentration Found (mg/ml) | | | |
|-------------------------------|-------------------|-----------------------------|------|------|------|
| | | 1 | 2 | 3 | Mean |
| 1.25 | Top | 1.33 | 1.34 | 1.35 | 1.34 |
| | Middle | 1.33 | 1.35 | 1.36 | 1.35 |
| | Bottom | 1.34 | 1.35 | 1.36 | 1.35 |
| 37.5 | Top | 40.5 | 39.5 | 39.5 | 39.8 |
| | Middle | 39.8 | 39.5 | 39.4 | 39.6 |
| | Bottom | 39.7 | 39.7 | 39.6 | 39.7 |
| 125 | Top | 132 | 134 | 132 | 132 |
| | Middle | 132 | 134 | 133 | 133 |
| | Bottom | 133 | 134 | 134 | 134 |

2.2 Stability of Test Material Formulations

| Nominal Concentration (mg/ml) | Concentration Found Initially (mg/ml) | Concentration Found After Storage for Fourteen Days | |
|-------------------------------|---------------------------------------|---|-----------------------------|
| | | (mg/ml) | (expressed as % of initial) |
| 12.5 | 12.4 | 12.6 | 102 |
| 37.5 | 39.7 | 36.1 | 91 |
| 125 | 133 | 124 | 94 |

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

**Appendix 20 (continued) Chemical Analysis of Test Material Formulations, Methods and
Results**

2.3 Verification of Concentration of Weekly Test Material Formulation

| Week Number | Nominal Concentration (mg/ml) | Concentration Found | |
|-------------|----------------------------------|---------------------|-----------------------------|
| | | (mg/ml) | (expressed as % of nominal) |
| 1 | 0 | ND | - |
| | 12.5 | 11.3 | 90 |
| | 37.5 | 35.7 | 95 |
| | 125 | 120 | 96 |
| 2 | 0 | ND | - |
| | 12.5 | 12.7 | 101 |
| | 37.5 | 38.3 | 102 |
| | 125 | 126 | 101 |
| 3 | 0 | ND | - |
| | 12.5 | 12.0 | 96 |
| | 37.5 | 35.9 | 96 |
| | 125 | 121 | 96 |
| 4 | 0 | ND | - |
| | 12.5 | 12.7 | 102 |
| | 37.5 | 38.0 | 101 |
| | 125 | 125 | 100 |
| 5 | 0 | ND | - |
| | 12.5 | 12.3 | 98 |
| | 37.5 | 37.2 | 99 |
| | 125 | 125 | 100 |
| 6 | 0 | ND | - |
| | 12.5 | 12.5 | 100 |
| | 37.5 | 36.3 | 97 |
| | 125 | 123 | 98 |
| 7 | 0 | ND | - |
| | 12.5 | 12.4 | 99 |
| | 37.5 | 35.4 | 94 |
| | 125 | 124 | 99 |
| 8 | 0 | ND | - |
| | 12.5 | 12.3 | 99 |
| | 37.5 | 37.9 | 101 |
| | 125 | 125 | 100 |

ND = none detected
- = not applicable

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Appendix 20 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

3. METHOD VALIDATION

3.1 Linearity

A range of standard solutions covering the concentration range 0 to 0.1608 mg/ml, were prepared and analysed.

The detector response was shown to be linear up to 0.1608 mg/ml.

| Standard Concentration (mg/ml) | Peak Area (units) |
|--------------------------------|-----------------------|
| 0.000 | 0.000 |
| 0.0536 | 1.528x10 ⁴ |
| 0.0858 | 2.433x10 ⁴ |
| 0.1072 | 3.013x10 ⁴ |
| 0.1286 | 3.613x10 ⁴ |
| 0.1608 | 4.502x10 ⁴ |
| Slope | 2.797x10 ⁵ |
| Intercept | 158.431 |
| Correlation Coefficient (r) | 1.000 |

The results are presented graphically in Figure 1.

3.2 Specificity

The diluent solvent acetone and a blank PEG 400 (control) were analysed. The results are shown in the following table:

| Sample | Concentration Found |
|-------------------|---------------------|
| Acetone | None detected |
| PEG 400 (control) | None detected |

Analysis of the solvent and a blank PEG 400 (control) produced no signal that interfered with the signal due to the test material.

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 20 (continued) Chemical Analysis of Test Material Formulations, Methods and Results****3.3 Accuracy**

Samples of PEG 400 were accurately fortified with known amounts of test material, and analysed:

| Fortification (mg/g) | Concentration Found (mg/g) | % Recovered | Mean Recovery (%) |
|----------------------|----------------------------|-------------|-------------------|
| 4.57 | 4.48 | 98 | 99 |
| 4.35 | 4.32 | 99 | |
| 242 | 238 | 98 | 98 |
| 263 | 259 | 99 | |

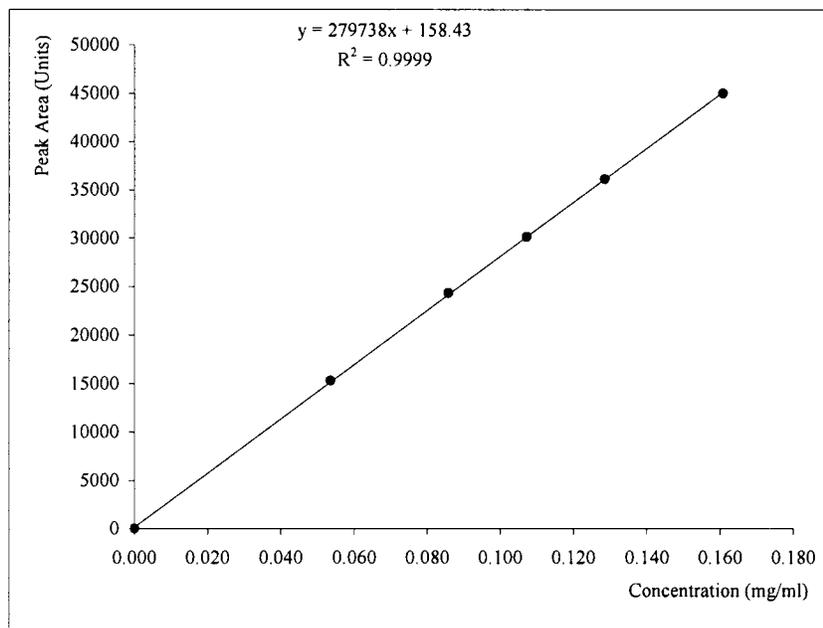
4. Conclusion

The analytical method has been satisfactorily validated in terms of linearity, specificity and accuracy for the purposes of the study. The results obtained during the analytical investigation of dose formulations showed that formulations at nominal concentrations of 12.5, 37.5 and 125 mg/ml were stable for up to fourteen days when stored at approximately 4°C in the dark. Formulations at nominal concentrations of 1.25, 37.5 and 125 mg/ml were homogeneous. The achieved concentrations of the formulations administered to the animals were 90 – 102 % of nominal concentration confirming the accuracy of the method of formulation.

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

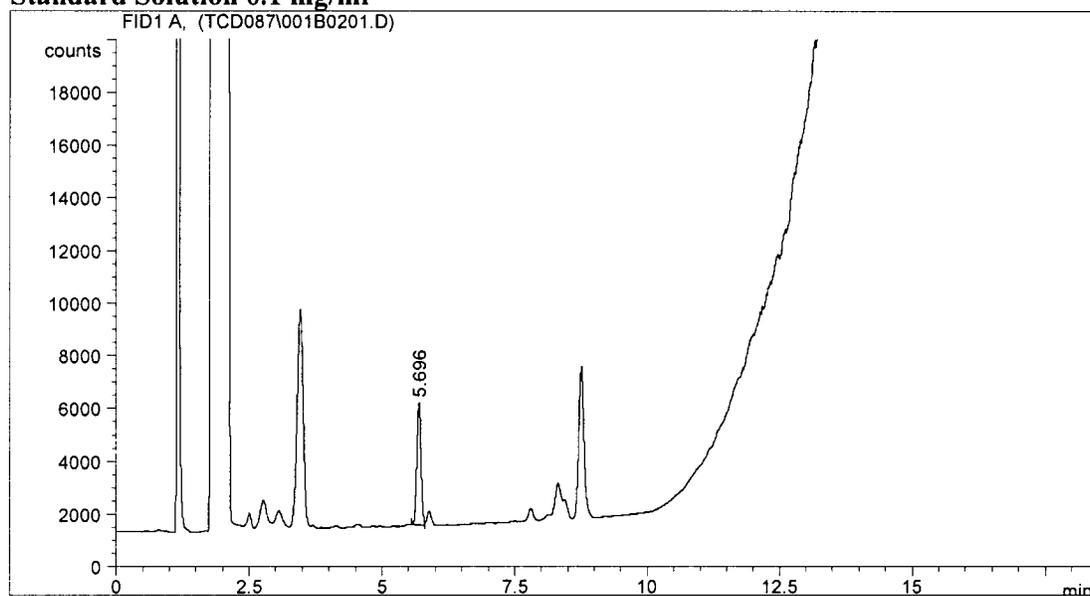
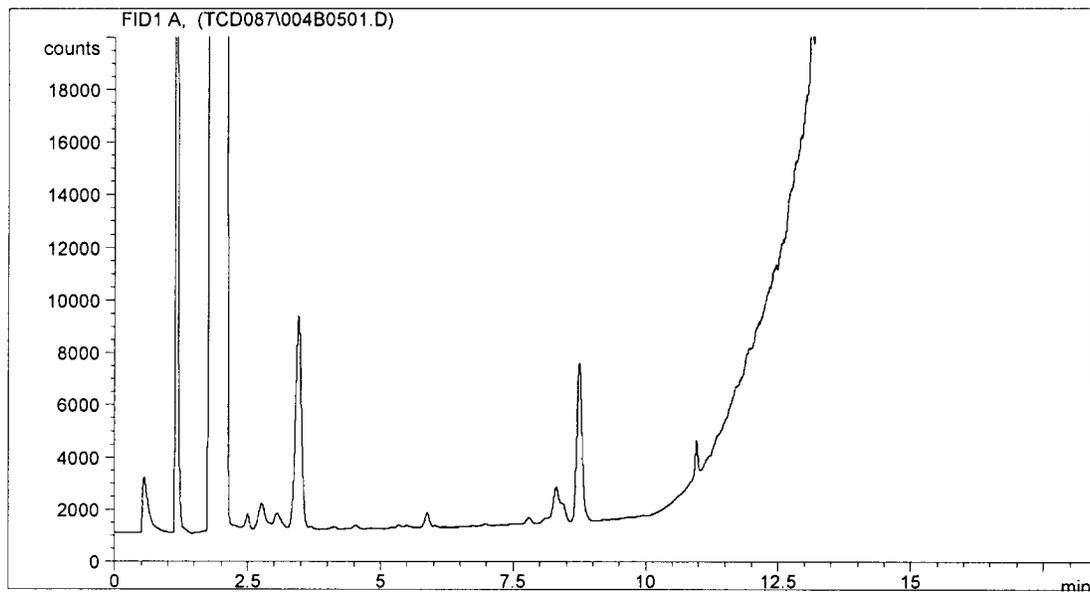
Appendix 20 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

Figure 1 Linearity of Detector Response



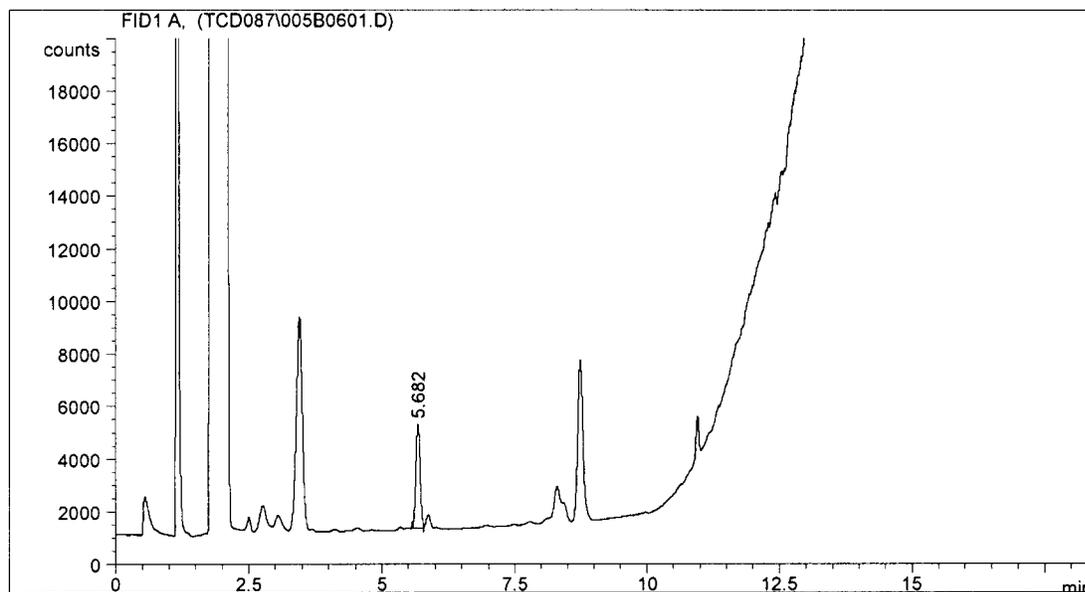
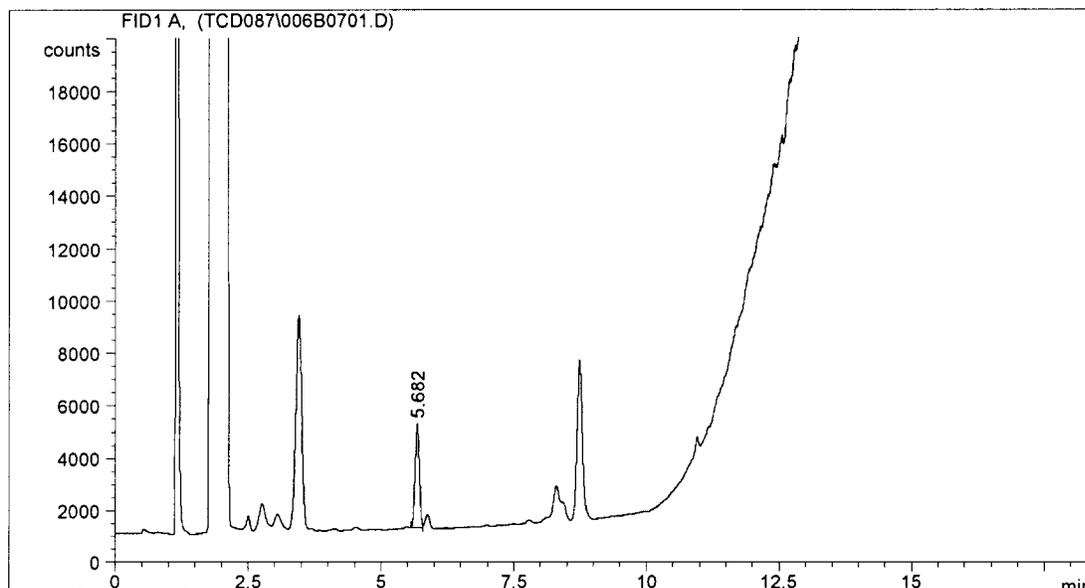
DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 20 (continued) Chemical Analysis of Test Material Formulations, Methods and Results**

Examples of the typical chromatography generated during this study are given below:

Standard Solution 0.1 mg/ml**Control**

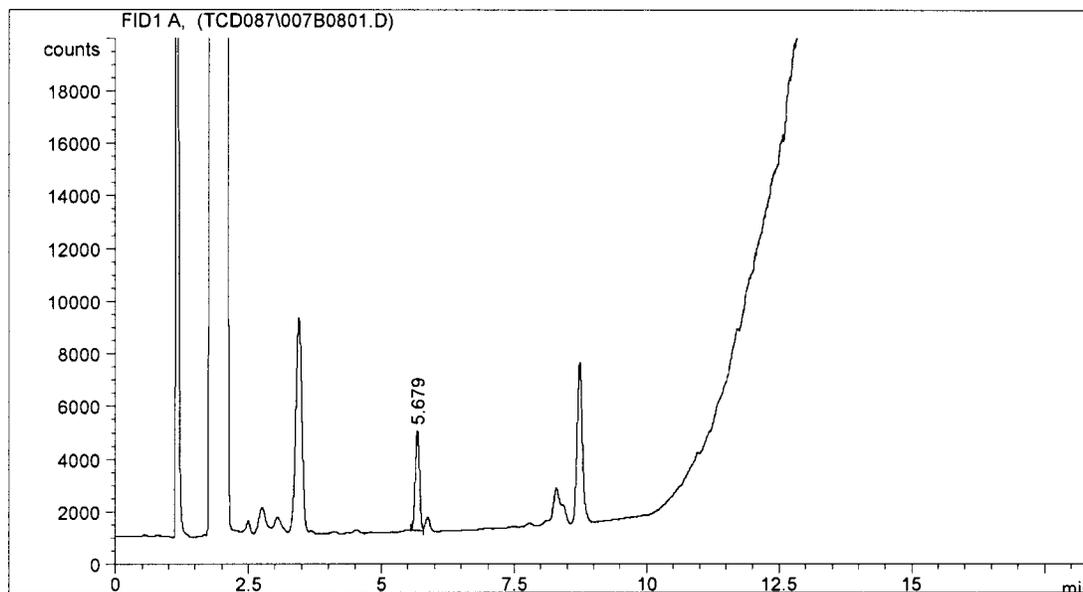
DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 20 (continued) Chemical Analysis of Test Material Formulations, Methods and Results**

Examples of the typical chromatography generated during this study are given below:

Test Material Formulation 12.5 mg/ml**Test Material Formulation 37.5 mg/ml**

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 20 (continued) Chemical Analysis of Test Material Formulations, Methods and Results**

Examples of the typical chromatography generated during this study are given below:

Test Material Formulation 125 mg/ml

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 21 Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat****1. INTRODUCTION**

This rangefinder was performed to establish the maximum tolerated dose level (up to 1000 mg/kg/day) of the test material following repeated oral (gavage) administration to the Sprague-Dawley CrI:CD[®] (SD) IGS BR strain rat, and to provide information for selection of dose levels for use in the subsequent main reproductive screening investigation. This fourteen day repeated dose investigation forms part of the overall reproductive screening study. Dosages of 1000, 500, 150 or 75 mg/kg/day were given to groups consisting of three male and three female rats. A control group of three male and three female rats was dosed with the vehicle (Polyethylene Glycol 400).

2. TEST MATERIAL AND FORMULATION

| | | |
|--------------------------|---|--|
| Sponsor's identification | : | Dibromomethane |
| Description | : | Clear colourless liquid |
| Purity | : | 99.4% |
| CAS number | : | 74-95-3 |
| Lot numbers | : | DBM082506 and 20050298 |
| Date received | : | 1 st September 2006 and 14 th September 2006 |
| Storage conditions | : | Room temperature in the dark |

Details relating to the preparation of formulations are presented in the methods section for the main reproductive screening investigation. As stability data for test material formulations had not been generated prior to the commencement of the range finder, fresh formulations was made each day and the animals were dosed within three hours of preparation. Achieved concentration of the test material formulations was not determined for this phase of the study.

A Certificate of Analysis is presented in Addendum 3.

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat

3. METHODS

3.1 Animals and Animal Husbandry

Fifteen male and fifteen female Sprague-Dawley Crl:CD[®] (SD) IGS BR rats, originally from Charles River (UK) Limited, Margate, Kent and acclimatised to the laboratory conditions, were used for this phase of the study. Animals were allocated to groups and given a unique number within the rangefinder by ear punching. At the start of treatment the males weighed 339 to 412 g and the females weighed 198 to 267 g.

The animals were housed in groups of three by sex in cages with environmental enrichment and free access to drinking water and food throughout the acclimatisation and treatment period. Details relating to caging, environmental enrichment and food and water were the same as that for main reproductive screening investigation.

The animals were housed in a single air-conditioned room within the Safepharm Barrier Maintained Rodent Facility and environmental conditions were as described in the main reproductive screening investigation. There were no deviations from the target ranges of $21 \pm 2^\circ\text{C}$ and $55 \pm 15\%$ temperature and relative humidity respectively.

3.2 Procedure

Animals were allocated to treatment groups as follows:

| Dose Level (mg/kg/day) | Treatment Volume (ml/kg) | Concentration (mg/ml) | Animal Numbers | |
|---------------------------|-----------------------------|--------------------------|----------------|---------|
| | | | Males | Females |
| 0 (Control) | 4 | 0 | 1-3 | 4-6 |
| 75 | 4 | 18.8 | 25-27 | 28-30 |
| 150 | 4 | 37.5 | 7-9 | 10-12 |
| 500 | 4 | 125 | 13-15 | 16-18 |
| 1000 | 4 | 250 | 19-21 | 22-24 |

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat**

The test material was administered daily by gavage using a suitable dosing cannula attached to a disposable plastic syringe at a dosage volume of 4 ml/kg bodyweight. Control animals were treated in an identical manner, receiving vehicle (Polyethylene Glycol 400) at the same volume dosage. Due to an adverse reaction to treatment at 1000 mg/kg/day, animals at these dosages were only dosed for three consecutive days. Control animals and animals receiving 75, 150 or 500 mg/kg/day were dosed for fourteen consecutive days. Animals receiving 75 mg/kg/day were added following the termination of animals receiving 1000 mg/kg/day and treatment started for these animals three days after the commencement of dosing for the other treatment groups.

The volume of test and control material administered to each animal was based on the most recent bodyweight and was adjusted at Days 4, 8 and 11.

3.3 Observations**3.3.1 Mortality**

Animals were examined for signs of ill health twice daily, early and late during the working period, throughout the study.

Animals at 1000 mg/kg/day killed on Day 4 due to the early termination of this dosage group were subjected to a full macroscopic necropsy.

3.3.2 Clinical Observations

All animals were examined for overt signs of toxicity, ill health or behavioural change immediately before dosing, immediately after dosing and one hour after dosing. All observations were recorded.

3.3.3 Bodyweight

Individual bodyweights were recorded on Days 1, 4, 8, 11 and 15 of the treatment period.

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat****3.3.4 Necropsy**

On completion of the treatment period, all animals were killed by cervical dislocation and immediately subjected to an internal and external macroscopic examination. No tissues were retained.

3.4 Evaluation of Data

Clinical observations, bodyweights, bodyweight change and necropsy data were examined for any adverse effects resulting from treatment. The data obtained were used to provide the basis for selection of dose levels for the main study. In view of the preliminary nature of this phase of the study and the small group size no statistical analyses were performed.

3.5 Deviation from Protocol Documented as a File Note

Due to a calculation error, male number 13 on the range-finder phase of the study was given a daily dose volume of 1.8 ml for the first three days of treatment. The animal should have received a daily dose volume of 1.4 ml during this period. This error was noticed on Day 4 when dose volumes were re-calculated for Day 4 bodyweights.

The intended dosage for this animal was 500 mg/kg/day. With the extra dose volume that animal 13 received, the dosage for this particular animal during the first three days was 550 mg/kg/day. There was no notable difference in the reaction to treatment of this animal and the other two males at 500 mg/kg/day that received the correct dosage. Following the range-finder phase of dosage of 500 mg/kg/day was subsequently selected for use on the main reproductive screening phase of the study.

There was an error in the above calculation for the dosage received by this animal. The animal received an extra 50 mg of test material (approximately 28.6%) giving a dosage of approximately 643 mg/kg/day during this period.

It is considered that the initial error in dosing of range-finder male number 13 during first three days of treatment had no adverse effect on the overall integrity of the study.

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat****4. RESULTS*****1000 mg/kg/day***

Treatment at 1000 mg/kg/day was associated with notable bodyweight loss and a decline in the clinical condition of all three males on Day 4 of the study. One male showed ataxia and piloerection and the other two males showed hunched posture; all three males also showed red/brown staining around the eyes. One female at 1000 mg/kg/day also showed ataxia and red/brown staining around the eyes and a slight bodyweight loss on Day 4. No clinical signs were apparent for the remaining two females at this dosage and there was no obvious adverse effects of treatment on bodyweight gain of these animals to Day 4.

This dosage was considered to be unsuitable for use in the main reproductive screening investigation and therefore the animals were terminated on Day 4 of the study, having received three consecutive daily doses. Macroscopic necropsy examination did not reveal any obvious cause for the decline in the condition of the animals.

75, 150 and 500 mg/kg/day

The incidence of clinical signs observed at 75, 150 or 500 mg/kg/day did not indicate any obvious adverse effect of treatment.

At 500 mg/kg/day, red staining of the cage tray paper was observed for males during Days 7-10; the significance of this observation is unclear but, as it did not persist and was not associated with any decline in the condition of the animals, it was considered not to preclude this dosage from further investigation.

There was no adverse effect of treatment on bodyweight gain at dosages of 75, 150 or 500 mg/kg/day.

An initial bodyweight loss to Day 4 was apparent for one male and one female at 150 mg/kg/day, although an initial loss was not apparent for the remaining animals at this dosage or for either sex at 500 mg/kg/day. Isolated incidences of bodyweight loss were observed for a few treated animals during the remainder of the study but were considered to reflect normal biological variation rather than an adverse effect of treatment.

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat**

All animals at 75, 150 or 500 mg/kg/day survived to scheduled termination and necropsy examination did not reveal any affect of treatment at any of these dosages.

5. CONCLUSION

A dosage of 1000 mg/kg/day was considered to be too high for use in the main reproductive screening investigation due to an adverse effect on bodyweight and the clinical condition of the animals, particularly males. Dosages of up to 500 mg/kg/day were considered to be well tolerated by both sexes.

The following dosages were subsequently used on the main reproductive screening phase of the study:

| | | |
|-------------------|---|--|
| High | : | 500 mg/kg/day |
| Intermediate dose | : | 150 mg/kg/day |
| Low dose | : | 50 mg/kg/day |
| Control | : | Vehicle only (Polyethylene Glycol 400) |

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

**Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral
(Gavage) Range-Finder in the Rat**

TABLES

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat

Table 1 Clinical Signs and Necropsy Finding for Males - Individual Observations

| Dose Level (mg/kg/day) | Animal Number | Clinical Signs (Days Observed) | Necropsy Observations |
|------------------------|---------------|---|------------------------------------|
| 0 (Control) | 1 | - | NAD |
| | 2 | - | NAD |
| | 3 | - | NAD |
| 75 | 25 | Increased salivation up to 10 minutes after dosing (12) | NAD |
| | 26 | - | NAD |
| | 27 | Increased salivation up to 10 minutes after dosing (14) | NAD |
| 150 | 7 | - | NAD |
| | 8 | - | NAD |
| | 9 | - | NAD |
| 500 | 13+ | Increased salivation up to 10 minutes after dosing (13) | NAD |
| | 14+ | Red/brown staining around eyes (5) | NAD |
| | 15+ | - | NAD |
| 1000 # | 19 | Piloerection (4) Ataxia (4) | NAD |
| | 20 | Red/brown staining around eyes (4) | NAD |
| | | Hunched posture (4) | |
| | 21 | Red/brown staining around eyes (4) | NAD |
| | | Hunched posture (4) | |
| | | | Red/brown staining around eyes (4) |

+ = red staining on cage tray liner (7-10)

= dosage terminated on Day 4

NAD = no abnormalities detected

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat

Table 2 Clinical Signs and Necropsy Finding for Females - Individual Observations

| Dose Level (mg/kg/day) | Animal Number | Clinical Signs (Days Observed) | Necropsy Observations |
|------------------------|---------------|--|-----------------------|
| 0 (Control) | 4 | Increased salivation up to 10 minutes after dosing (9) | NAD |
| | 5 | Noisy respiration (9) | NAD |
| | 6 | - | NAD |
| 75 | 28 | Noisy respiration up to 10 minutes after dosing (14) | NAD |
| | 29 | - | NAD |
| | 30 | - | NAD |
| 150 | 10 | - | NAD |
| | 11 | - | NAD |
| | 12 | - | NAD |
| 500 | 16 | - | NAD |
| | 17 | - | NAD |
| | 18 | - | NAD |
| 1000 # | 22 | - | NAD |
| | 23 | Ataxia (4) Red/brown staining around eyes (4) | NAD |
| | 24 | - | NAD |

= dosage terminated on Day 4
 NAD = no abnormalities detected

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat

Table 3 Bodyweights and Bodyweight Change for Males - Individual Values

| Dose Level (mg/kg/day) | Animal Number | Bodyweight (g) Day | | | | | | | Bodyweight Change (g) during Days | | | | | | |
|---------------------------|------------------|--------------------|-----|-----|-----|-----|-----|-----|-----------------------------------|-------|-----|------|------|--|--|
| | | 1 | 4 | 8 | 11 | 15 | 1-4 | 4-8 | 8-11 | 11-15 | 1-8 | 1-11 | 1-15 | | |
| 0 (Control) | 1 | 366 | 376 | 404 | 405 | 417 | 10 | 28 | 1 | 12 | 38 | 39 | 51 | | |
| | 2 | 364 | 379 | 398 | 409 | 424 | 15 | 19 | 11 | 15 | 34 | 45 | 60 | | |
| | 3 | 375 | 382 | 405 | 421 | 431 | 7 | 23 | 16 | 10 | 30 | 46 | 56 | | |
| 75 | 25 | 365 | 385 | 408 | 415 | 427 | 20 | 23 | 7 | 12 | 43 | 50 | 62 | | |
| | 26 | 341 | 350 | 365 | 372 | 385 | 9 | 15 | 7 | 13 | 24 | 31 | 44 | | |
| | 27 | 359 | 381 | 398 | 399 | 409 | 22 | 17 | 1 | 10 | 39 | 40 | 50 | | |
| 150 | 7 | 369 | 362 | 382 | 401 | 413 | -7 | 20 | 19 | 12 | 13 | 32 | 44 | | |
| | 8 | 343 | 349 | 363 | 374 | 376 | 6 | 14 | 11 | 2 | 20 | 31 | 33 | | |
| | 9 | 349 | 366 | 391 | 401 | 409 | 17 | 25 | 10 | 8 | 42 | 52 | 60 | | |
| 500 | 13 | 412 | 423 | 445 | 464 | 459 | 11 | 22 | 19 | -5 | 33 | 52 | 47 | | |
| | 14 | 376 | 383 | 401 | 411 | 414 | 7 | 18 | 10 | 3 | 25 | 35 | 38 | | |
| | 15 | 362 | 366 | 384 | 397 | 404 | 4 | 18 | 13 | 7 | 22 | 35 | 42 | | |
| 1000 | 19 | 387 | 338 | | | | -49 | | | | | | | | |
| | 20 | 369 | 327 | | | | -42 | | | | | | | | |
| | 21 | 339 | 303 | | | | -36 | | | | | | | | |

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Dibromomethane: Preliminary Fourteen Day Repeated Dose Oral (Gavage) Range-Finder in the Rat

Table 4 Bodyweights and Bodyweight Change for Females - Individual Values

| Dose Level (mg/kg/day) | Animal Number | Bodyweight (g) Day | | | | | | | Bodyweight Change (g) during Days | | | | | | |
|---------------------------|------------------|--------------------|-----|-----|-----|-----|-----|-----|-----------------------------------|-------|-----|------|------|--|--|
| | | 1 | 4 | 8 | 11 | 15 | 1-4 | 4-8 | 8-11 | 11-15 | 1-8 | 1-11 | 1-15 | | |
| 0 (Control) | 4 | 198 | 205 | 216 | 217 | 221 | 7 | 11 | 1 | 4 | 18 | 19 | 23 | | |
| | 5 | 253 | 258 | 259 | 259 | 261 | 5 | 1 | 0 | 2 | 6 | 6 | 8 | | |
| | 6 | 218 | 229 | 234 | 237 | 242 | 11 | 5 | 3 | 5 | 16 | 19 | 24 | | |
| 75 | 28 | 238 | 251 | 252 | 246 | 248 | 13 | 1 | -6 | 2 | 14 | 8 | 10 | | |
| | 29 | 256 | 264 | 273 | 267 | 278 | 8 | 9 | -6 | 11 | 17 | 11 | 22 | | |
| | 30 | 234 | 247 | 250 | 251 | 253 | 13 | 3 | 1 | 2 | 16 | 17 | 19 | | |
| 150 | 10 | 210 | 212 | 219 | 233 | 231 | 2 | 7 | 14 | -2 | 9 | 23 | 21 | | |
| | 11 | 204 | 208 | 221 | 217 | 223 | 4 | 13 | -4 | 6 | 17 | 13 | 19 | | |
| | 12 | 260 | 252 | 257 | 258 | 259 | -8 | 5 | 1 | 1 | -3 | -2 | -1 | | |
| 500 | 16 | 237 | 250 | 257 | 249 | 251 | 13 | 7 | -8 | 2 | 20 | 12 | 14 | | |
| | 17 | 251 | 267 | 275 | 276 | 278 | 16 | 8 | 1 | 2 | 24 | 25 | 27 | | |
| | 18 | 267 | 280 | 287 | 296 | 295 | 13 | 7 | 9 | -1 | 20 | 29 | 28 | | |
| 1000 | 22 | 233 | 235 | | | | 2 | | | | | | | | |
| | 23 | 260 | 256 | | | | -4 | | | | | | | | |
| | 24 | 213 | 231 | | | | 18 | | | | | | | | |

ADDENDA

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Addendum 1 Certificate of Analysis of Diet Used



Return to Certified Analysis Retrieval

Product Code: 5002
 Product Desc: CERTIFIED RODENT DIET
 Lab Number: L0618574-1
 Lot Code: JUN 16 06 1A
 Entered: 6/28/2006

| Assay | Analysis | Units | |
|---------------------------|-----------------------|---------------------------|----------------|
| PROTEIN | 20.8 | % | |
| FAT (ACID HYDRO.) | 5.6 | % | |
| FIBER (CRUDE) | 4.37 | % | |
| ARSENIC | <0.20 | PPM | |
| CADMIUM | 0.0569 | PPM | |
| CALCIUM | 0.9388 | % | |
| LEAD | 0.232 | PPM | |
| MERCURY | LESS THAN 0.025 | PPM | |
| PHOSPHORUS | 0.7289 | % | |
| SELENIUM | 0.306 | PPM | |
| | | | |
| ORGANOPHOSPHATES | PPM | ORGANOPHOSPHATES | PPM |
| Diazinon | LESS THAN 0.02 | Disulfoton | LESS THAN 0.02 |
| Ethion | LESS THAN 0.02 | Malathion | LESS THAN 0.02 |
| Methyl Parathion | LESS THAN 0.02 | Parathion | LESS THAN 0.02 |
| Thimet | LESS THAN 0.02 | Thiodan | LESS THAN 0.02 |
| Trithion | LESS THAN 0.02 | | |
| | | | |
| PESTICIDES AND PCB | PPM | PESTICIDES AND PCB | PPM |
| Aldrin | LESS THAN 0.02 | Alpha-BHC | LESS THAN 0.02 |
| Beta-BHC | LESS THAN 0.02 | Chlordane | LESS THAN 0.02 |
| DDE | LESS THAN 0.02 | DDT | LESS THAN 0.02 |
| Delta-BHC | LESS THAN 0.02 | Dieldrin | LESS THAN 0.02 |
| Endrin | LESS THAN 0.02 | HCB | LESS THAN 0.02 |
| Heptachlor | LESS THAN 0.02 | Heptachlor Epoxide | LESS THAN 0.02 |
| Lindane | LESS THAN 0.02 | Methoxychlor | LESS THAN 0.02 |
| Mirex | LESS THAN 0.02 | PCB | LESS THAN 0.15 |
| | | | |
| AFLATOXINS | PPB Aflatoxins | LESS THAN 5 | |

No notes.

For additional information, please contact:

- 1) Customer Service at (314) 982-1310 – for assay methodology
- 2) Dr. Dorrance Haught at (314) 317-5178 – for nutritional interpretation
- 3) Richmond, IN Manufacturing Plant at (765) 962-9561 – all other questions

The term "Less Than" is used to signify the lower limit of quantitation of the procedure under the conditions employed.
 The use of the term "Less Than" does not imply that traces of analyte were present.

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Addendum 1 (continued) Certificate of Analysis of Diet Used



Return to Certified Analysis Retrieval

Product Code: 5002
 Product Desc: CERTIFIED RODENT DIET
 Lab Number: L0619938-2
 Lot Code: JUL 17 06 28
 Entered: 7/31/2006

| Assay | Analysis | Units |
|-------------------|-----------------|-------|
| PROTEIN | 21.4 | % |
| FAT (ACID HYDRO.) | 5.54 | % |
| FIBER (CRUDE) | 4.05 | % |
| ARSENIC | LESS THAN 0.2 | PPM |
| CADMIUM | 0.0507 | PPM |
| CALCIUM | 0.8607 | % |
| LEAD | 0.235 | PPM |
| MERCURY | LESS THAN 0.025 | PPM |
| PHOSPHORUS | 0.7461 | % |
| SELENIUM | 0.302 | PPM |

| ORGANOPHOSPHATES | PPM | ORGANOPHOSPHATES | PPM |
|------------------|----------------|------------------|----------------|
| Diazinon | LESS THAN 0.02 | Disulfoton | LESS THAN 0.02 |
| Ethion | LESS THAN 0.02 | Malathion | LESS THAN 0.02 |
| Methyl Parathion | LESS THAN 0.02 | Parathion | LESS THAN 0.02 |
| Thimet | LESS THAN 0.02 | Thiodan | LESS THAN 0.02 |
| Trithion | LESS THAN 0.02 | | |

| PESTICIDES AND PCB | PPM | PESTICIDES AND PCB | PPM |
|--------------------|----------------|--------------------|----------------|
| Aldrin | LESS THAN 0.02 | Alpha-BHC | LESS THAN 0.02 |
| Beta-BHC | LESS THAN 0.02 | Chlordane | LESS THAN 0.02 |
| DDE | LESS THAN 0.02 | DDT | LESS THAN 0.02 |
| Delta-BHC | LESS THAN 0.02 | Dieldrin | LESS THAN 0.02 |
| Endrin | LESS THAN 0.02 | HCB | LESS THAN 0.02 |
| Heptachlor | LESS THAN 0.02 | Heptachlor Epoxide | LESS THAN 0.02 |
| Lindane | LESS THAN 0.02 | Methoxychlor | LESS THAN 0.02 |
| Mirex | LESS THAN 0.02 | PCB | LESS THAN 0.15 |

| AFLATOXINS | PPB Aflatoxins | LESS THAN 5 |
|------------|----------------|-------------|
| | | |

No notes.

For additional information, please contact

- 1) Customer Service at (314) 982-1310 – for assay methodology
- 2) Dr. Dorrance Haught at (314) 317-5178 – for nutritional interpretation
- 3) Richmond, IN Manufacturing Plant at (765) 962-9561 – all other questions

The term "Less Than" is used to signify the lower limit of quantitation of the procedure under the conditions employed
 The use of the term "Less Than" does not imply that traces of analyte were present

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Addendum 2 Typical Water Quality Characteristics

| WATER SUPPLY ZONE ZDB13 ALVASTON | | | | | | | | | |
|---|----------------|-----------------------|-------------------|--------------------------------------|----------|---------|---------------------|--------------------------|---------|
| REPORTING PERIOD: 01/01/2004 - 31/12/2004 | | | | | | | | | |
| PARAMETER | ANALYSIS UNITS | PLANNED NO OF SAMPLES | NO. SAMPLES TAKEN | CONCENTRATION OR VALUE (ALL SAMPLES) | | | PCV | SAMPLES CONTRAVENING PCV | |
| | | | | MINIMUM | AVERAGE | MAXIMUM | | NUMBER | PERCENT |
| 1,2 Dichloroethane | µg/l | 8 | 8 | < 0.120 | < 0.120 | 0.120 | 3 | 0 | 0.00 |
| Aldrin | µg/l | 8 | 8 | < 0.002 | < 0.002 | 0.002 | 0.03 | 0 | 0.00 |
| Aluminium | µg/l | 52 | 52 | < 5.000 | < 10.231 | 43.000 | 200 | 0 | 0.00 |
| Antimony | µg/l | 8 | 8 | < 0.240 | < 0.561 | 1.000 | 5 | 0 | 0.00 |
| Arsenic | µg/l | 8 | 8 | < 0.500 | < 0.563 | 1.000 | 10 | 0 | 0.00 |
| Benzene | µg/l | 8 | 8 | < 0.150 | < 0.150 | 0.150 | 1 | 0 | 0.00 |
| Benzo 3,4 Pyrene | ng/l | 8 | 8 | < 0.001 | < 0.001 | 0.001 | 10 | 0 | 0.00 |
| Boron | µg/l | 8 | 8 | 0.016 | 0.029 | 0.042 | 1000 | 0 | 0.00 |
| Bromate | µg/l | 8 | 8 | < 0.800 | < 0.800 | 0.800 | 10 | 0 | 0.00 |
| Cadmium | µg/l | 8 | 8 | < 0.230 | < 0.268 | 0.400 | 5 | 0 | 0.00 |
| Chromium | µg/l | 8 | 8 | < 0.340 | < 0.484 | 1.000 | 50 | 0 | 0.00 |
| Coliform Bacteria | No./100 ml | 180 | 1 | 0.000 | 0.000 | 0.000 | 0 | 0 | 0.00 |
| Colour | mg/l | 26 | 26 | < 0.400 | < 0.977 | 1.900 | 20 | 0 | 0.00 |
| Copper | µg/l | 8 | 8 | 0.002 | 0.019 | 0.064 | 2000 | 0 | 0.00 |
| Cyanide | µg/l | 8 | 8 | < 0.220 | < 0.378 | 0.590 | 50 | 0 | 0.00 |
| Dieldrin | µg/l | 8 | 8 | < 0.002 | < 0.002 | 0.002 | 0.03 | 0 | 0.00 |
| E. coli | No./100 ml | 180 | 180 | 0.000 | 0.000 | 0.000 | 0 | 0 | 0.00 |
| Enterococci | No./100 ml | 8 | 8 | 0.000 | 0.000 | 0.000 | 0 | 0 | 0.00 |
| Fluoride | µg/l | 8 | 8 | 0.220 | 0.321 | 0.420 | 15000 | 0 | 0.00 |
| Gross Alpha Activity | Bq/l | 8 | 8 | < 0.020 | < 0.033 | 0.050 | 0.1 | 0 | 0.00 |
| Gross Beta Activity | Bq/l | 8 | 8 | 0.050 | 0.200 | 0.820 | 1 | 0 | 0.00 |
| Heptachlor | µg/l | 8 | 8 | < 0.002 | < 0.002 | 0.002 | 0.03 | 0 | 0.00 |
| Hepachlor epoxide | µg/l | 8 | 8 | < 0.002 | < 0.002 | 0.002 | 0.03 | 0 | 0.00 |
| Iron | µg/l | 52 | 52 | < 7.000 | < 39.731 | 203.000 | 200 | 1 | 1.92 |
| Lead | µg/l | 8 | 9 | < 1.000 | < 1.999 | 6.590 | 25 | 0 | 0.00 |
| Manganese | µg/l | 52 | 52 | < 1.500 | 2.513 | 18.000 | 50 | 0 | 0.00 |
| Mercury | µg/l | 8 | 8 | < 0.000 | < 0.013 | 0.015 | 1 | 0 | 0.00 |
| Nickel | µg/l | 8 | 8 | < 1.400 | < 2.113 | 3.500 | 20 | 0 | 0.00 |
| Nitrate | mg/l | 8 | 8 | 8.900 | 13.838 | 21.500 | 50 | 0 | 0.00 |
| Nitrite | mg/l | 8 | 8 | < 0.002 | < 0.004 | 0.010 | 0.5 | 0 | 0.00 |
| Odour | Dilution No | 26 | 26 | 0.000 | 0.000 | 0.000 | 3 at 25°C | 0 | 0.00 |
| PAH | µg/l | 8 | 8 | 0.000 | 0.000 | 0.000 | 0.1 | 0 | 0.00 |
| pH | pH value | 52 | 52 | 7.180 | 7.573 | 8.000 | Max 9.5, Min 6.5 | 0 | 0.00 |
| Selenium | µg/l | 8 | 8 | < 0.530 | < 0.786 | 1.000 | 10 | 0 | 0.00 |
| Sodium | mg/l | 8 | 8 | 14.000 | 24.625 | 32.000 | 200 | 0 | 0.00 |
| Taste | Dilution No | 26 | 26 | 0.000 | 0.000 | 0.000 | 3 at 25°C | 0 | 0.00 |
| Tetrachloroethene and Trichloroethene | µg/l | 8 | 8 | 0.000 | 0.041 | 0.190 | 10 | 0 | 0.00 |
| Tetrachloromethane | µg/l | 8 | 8 | < 0.000 | < 0.030 | 0.040 | 3 | 0 | 0.00 |
| Total Pesticides | µg/l | 8 | 8 | 0.000 | 0.000 | 0.000 | 0.5 | 0 | 0.00 |
| Total Trihalomethanes | µg/l | 8 | 8 | 28.000 | 44.525 | 72.200 | 100 | 0 | 0.00 |
| Turbidity | NTU | 52 | 52 | < 0.030 | < 0.132 | 0.450 | 4 | 0 | 0.00 |
| Free Chlorine | mg/l | 180 | 180 | 0.030 | 0.236 | 0.570 | - | 0 | 0.00 |
| Total Chlorine | mg/l | 180 | 180 | < 0.010 | < 0.153 | 0.390 | - | 0 | 0.00 |
| Ammonium | mg/l | 26 | 26 | < 0.020 | < 0.033 | 0.303 | 0.5 | 0 | 0.00 |
| Chloride | mg/l | 8 | 8 | 18.700 | 26.050 | 30.900 | 250 | 0 | 0.00 |
| Clostridium perfringens | No./100 ml | 26 | 26 | 0.000 | 0.000 | 0.000 | 0 | 0 | 0.00 |
| Coliform Bacteria | No./100 ml | 180 | 180 | 0.000 | 0.006 | 1.000 | 0 | 1 | 0.56 |
| Colony Count After 72 Hours at 22°C | No./100 ml | 52 | 57 | 0.000 | 8.088 | 194.000 | - | 0 | 0.00 |
| Colony Count After 48 Hours at 37°C | No./100 ml | 52 | 57 | 0.000 | 12.263 | 380.000 | - | 0 | 0.00 |
| Conductivity | µS/cm at 20°C | 26 | 29 | 292.000 | 437.276 | 549.000 | 2500 | 0 | 0.00 |
| Nitrite/Nitrate Calculated | mg/l | 8 | 8 | < 0.260 | < 0.298 | 0.430 | < 1 | 0 | 0.00 |
| Sulphate | mg/l | 8 | 8 | 58.600 | 69.625 | 80.100 | 250 | 0 | 0.00 |
| Total Organic Carbon | mg/l | 8 | 8 | 1.220 | 1.675 | 1.990 | - | 0 | 0.00 |

PCV = Prescribed concentration or value for mandatory parameters and specified limit or value for non-mandatory parameters (indicators and disinfectants)

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Addendum 3 Certificate of Analysis for Dibromomethane



SafePharm Laboratories Ltd
Shardlow Business Park
London Road, Shardlow
Derbyshire DE72 2GD
Tel: 01332 792896 Fax: 01332 799018
Website: www.safepharm.co.uk

MIXING AND ANALYSIS OF TEST MATERIAL SAMPLES

CERTIFICATE OF ANALYSIS

| | | |
|-----------------------|--|--------------------------------|
| TEST MATERIAL | : Dibromomethane | |
| PROJECT NUMBER | : 0466/0267 | |
| CO-SPONSORS | : Bromine Compounds Ltd. | Albemarle Corporation |
| | Makleff House | Health, Safety and Environment |
| | P.O.B. 180 | 451 Florida Street |
| | BEER-SHEVA 84101 | Baton Rouge |
| | ISRAEL | LA 70801 |
| | | UNITED STATES OF AMERICA |
| TEST DATES | : 14 September 2006 to 28 September 2006 | |

Test Material Details:

| | | |
|---------------------------|---------------------------------|-------------------------------|
| Supplier | : Bromine Compounds Ltd | Albemarle Corporation |
| Name | : Dibromomethane | Dibromomethane |
| Description | : clear, colourless liquid | clear, colourless liquid |
| Lot number | : 20050298 | DBM082506 |
| Date Received | : 12 September 2006 | 01 September 2006 |
| Storage Conditions | : room temperature, in the dark | room temperature, in the dark |

Testing Details:

The above two test materials were mixed in equal proportions and the purity of the resulting mixture determined by gas chromatography (GC) area normalisation. The purity was determined to be 99.4%.

Analytical Conditions:

| | |
|--|--|
| Column | : ZB-624 (30 m x 0.25 mm id, 1.40 µm film) |
| Oven temperature program | : initial temperature : 40°C rate: 5°C/minute final temperature: 260°C for 5 minutes |
| Injector temperature | : 250°C |
| Flame ionisation detector temperature | : 300°C |
| Injection volume | : 1 µl |
| Retention time | : approximately 9.5 minutes for Dibromomethane |

DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

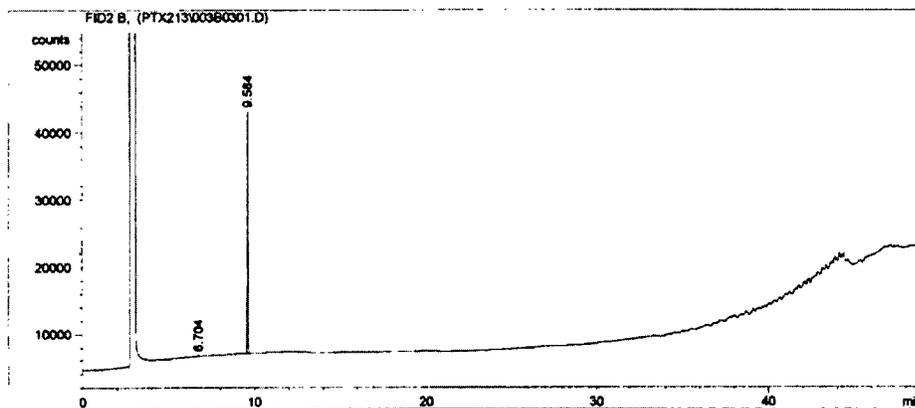
Addendum 3 (continued) Certificate of Analysis for Dibromomethane



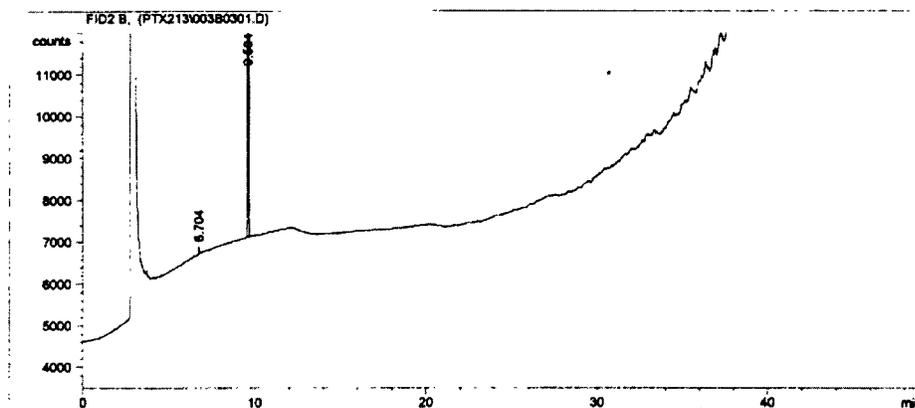
SafePharm Laboratories Ltd
Shardlow Business Park
London Road, Shardlow
Derbyshire DE72 2GD
Tel: 01332 792896 Fax: 01332 799018
Website: www.safepharm.co.uk

Typical Chromatography

Sample Solution, 6.14×10^3 mg/l in Methanol



Sample Solution (Expanded Scale)



DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT**Addendum 3 (continued) Certificate of Analysis for Dibromomethane**

SafePharm Laboratories Ltd
Shardlow Business Park
London Road, Shardlow
Derbyshire DE72 2GD
Tel: 01332 792896 Fax: 01332 799018
Website: www.safepharm.co.uk

I the undersigned, hereby declare that this certificate of analysis accurately reflects the original data generated in SPL Project Number 0466/0267.

This study was performed in compliance with the UK GLP Regulations 1999 (as amended in 2004) and this certificate accurately reflects the results obtained. The original data and the Certificate of Analysis will be kept for five years in the archives of Safepharm Laboratories Ltd.

Signed:  Date: **02 NOV 2006**
B J O'Connor BSc (Hons) MRSC
Study Director

Studies of this type are monitored and reported by Safepharm Laboratories Quality Assurance Unit as part of a routine sampling programme: 14, 26 September 2006.

The certificate was audited on 02 November 2006 by Safepharm Laboratories Quality Assurance Unit. It is considered to be an accurate account of the data generated and of the results produced.

Signed:  Date: **02 NOV 2006**
For Safepharm Quality Assurance Unit

**DIBROMOMETHANE : ORAL (GAVAGE) REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING
TEST IN THE RAT**

Addendum 4 Statement of GLP Compliance in Accordance with Directive 2004/9/EC



**THE DEPARTMENT OF HEALTH OF THE GOVERNMENT
OF THE UNITED KINGDOM**

GOOD LABORATORY PRACTICE

**STATEMENT OF COMPLIANCE
IN ACCORDANCE WITH DIRECTIVE 2004/9/EC**

| LABORATORY | TEST TYPE |
|---|---|
| SafePharm Laboratories Ltd. Shardlow Business Park London Road Shardlow Derby DE72 2GD | Analytical Chemistry Environmental Fate Environmental Toxicity Mutagenicity Phys/Chem Testing Toxicology |

DATE OF INSPECTION

30th August 2005

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of the UK GLP Compliance Programme.

At the time of inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

A handwritten signature in black ink that reads 'Bryan J. Wright' with the date '21/11/05.' written below it.

Mr. Bryan J. Wright
Head, UK GLP Monitoring Authority

SAFEPHARM LABORATORIES LIMITED

AMENDMENT TO PROTOCOL

AMENDMENT NUMBER: One

PROTOCOL TITLE: Chromosome Aberration Test in Human Lymphocytes: *In Vitro*

TEST MATERIAL: Dibromoethane

PROJECT NUMBER: 0466/0262

CO-SPONSORS: Bromine Compounds Ltd.
Makleff House
P.O.B.180
BEER-SHEEVA 84101
ISRAEL

Albemarle Corporation
Health, Safety and Enviroment
451 Florida Street
Baton Rouge
LA 70801
UNITED STATES OF AMERICA

AMENDMENT: Due to the departure of the current Study Director, Ms N Wright, from Safepharm Laboratories Ltd., R Durward will assume the role of Study Director.

P C Jenkinson Date: 24 APR 2007.....
Director of Genetic Toxicology

As Study Director, I accept that I will be responsible for the accuracy of the GLP Compliance Statement in the final report in respect of the whole study, including any work completed before the date of this Amendment. I will review the study plan/protocol and any amendments, correspondence, QA reports and any data collected prior to this date, to ensure that I am aware of the technical and GLP compliance status of the whole study.

R Durward Date: 24 APR 2007.....
Study Director

SAFEPHARM LABORATORIES LIMITED

C U R R I C U L U M V I T A E

NAME: ROBERT DURWARD

PRESENT POSITION: Deputy Head
(since 1993) Department of Genetic Toxicology
SafePharm Laboratories Limited
Shardlow Business Park
Shardlow
Derbyshire
DE72 2GD

Responsibilities include to assist in the running of the department, act as Study Director for allocated studies and to supervise and assist in the training and supervision of junior members of staff. Animal Project Licence holder for the Department

EDUCATION:

1974 - 1977: Trent Polytechnic, Nottingham
H.N.C. Applied Biology (Pharmacology)

1972 - 1974: Oakham Sixth Form College, Oakham, Rutland,
Leicestershire
G.C.E. 'A' Levels: Biology, Chemistry

1970 - 1972: Richmond Grammar School, Yorkshire
G.C.E. 'O' Level: English Language, English Literature,
Mathematics, Biology, Physics, Chemistry, Geography,
Woodwork

1967 - 1969: Windsor Boys School, Hamm, West Germany

PROFESSIONAL EXPERIENCE:

2007 – Date: Deputy Head
Department of Genetic Toxicology
SafePharm Laboratories Limited

1993 - 2006: Senior Genetic Toxicologist
Department of Genetic Toxicology
SafePharm Laboratories Limited

1991 - 1993: Study Director
Department of Genetic Toxicology
SafePharm Laboratories Limited

1990 - 1991: Study Supervisor
Department of Genetic Toxicology
SafePharm Laboratories Limited

-2-

1978 - 1990: Senior Technician
Genetic Toxicology
Boots Company Limited

1977 - 1978: Technician Grade IV
Boots Company Limited
Gastric Secretion, Rheumatism Research

1974 - 1977 Junior Technician Grade III
Boots Company Limited
Drug Metabolism

ADDITIONAL TRAINING:

Flow Tissue Culture Course, February 1978

Cytogenetics Course, Swansea, February 1996

Institute of Biology Course Modules 1, 2 and 5 for Animal (Scientific Procedures) Act 1986,
April 2004

CONFIDENTIAL

SIGNED:  DATE: 9 Jan. 2007 INITIALLED: 

R Durward HNC
DEPUTY HEAD OF GENETIC TOXICOLOGY