Materials and methods: Glyphosate acid (98.7%) was fed *ad libitum* to four groups of 50 male and 50 female Sprague-Dawley rats for approximately 26 months. The dietary levels of glyphosate administered during the first week of the study were 30, 100 and 300 ppm corresponding with a daily intake of 3.05 and 3.37 mg/kg bw, 10.30 and 11.22 mg/kg bw and 31.49 and 34.02 mg/kg bw for males and females, respectively. These daily doses were maintained for the remainder of the study. Diet analyses were performed prior to study initiation to confirm mixing homogeneity and stability. During the study the diets were analysed at preparation and at the end of the feeding period for weeks 1, 2, 3, 4, 6, 12, 16, 24, 36, 48, 60, 72, 84, 96 and 111.

All rats were observed twice daily for mortality and toxic signs. Body weights and food consumption were determined at pre-test, weekly for 14 weeks and bi-weekly thereafter. Water consumption was determined for 10 rats/sex/group for two separate three-day periods at 18 and 24 months.

Blood and urine samples were collected at months 4, 8, 12, 18 and 24 from 10 rats/sex/group. The haematology parameters measured were total erythrocyte count, total leukocyte count, platelet count, haematocrit, haemoglobin and leukocyte differential formula. The blood biochemistry parameters measured were albumin, globulin, total protein, blood urea nitrogen, total bilirubin, direct bilirubin, glucose, transaminases (ALT and AST), alkaline phosphatase, lactic acid dehydrogenase, cholesterol, calcium and potassium. Urinalysis included appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, blood and microscopic analysis of the sediment.

Complete necropsies were performed on all rats that died or were sacrificed during or at the end of the study. Organ weights were recorded for adrenals, brain, heart, kidneys, liver, testes/ovaries, pituitary, spleen and thyroid. The tissues preserved for histopathology were aorta, adrenals, bone, bone marrow, brain, epididymides, caecum, colon, duodenum, oesophagus, eyes with optic nerves, gonads, Harderian glands, gall bladder, heart, ileum, jejunum, kidneys, liver, lungs (with bronchi), lymph nodes, mammary gland, muscle, ovaries, pancreas, pituitary, prostate, rectum, sciatic nerve, skin, spinal cord (cervical and thoracic), spleen, stomach, salivary gland, seminal vesicles, testes, thymus, thyroid/parathyroid, tissues with lesions and/or abnormal masses, trachea, ureter, uterus and urinary bladder.

Findings: Analysis of the neat test material at several weeks during the study indicated that it was stable. Analysis of glyphosate in the diet prior to study initiation and during
the study indicated that it was homogeneously mixed and that it remained stable during a one-week feeding period. Day 1 and day 7 diets contained an average of 95.4% of the intended concentrations over the study period.

Survival was similar for the control and treated groups (table 1).

**Table 1. Cumulative mortality of rats from all groups**

<table>
<thead>
<tr>
<th>Dose (mg/kg bw/day)</th>
<th>Males 18 months</th>
<th>Males 24 months</th>
<th>Males End</th>
<th>Females 18 months</th>
<th>Females 24 months</th>
<th>Females End</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8/50</td>
<td>20/50</td>
<td>35/50</td>
<td>3/50</td>
<td>24/50</td>
<td>32/50</td>
</tr>
<tr>
<td>3</td>
<td>5/50</td>
<td>22/50</td>
<td>24/50</td>
<td>4/50</td>
<td>19/50</td>
<td>27/50</td>
</tr>
<tr>
<td>10</td>
<td>6/50</td>
<td>27/50</td>
<td>34/50</td>
<td>3/50</td>
<td>18/50</td>
<td>20/50</td>
</tr>
<tr>
<td>30</td>
<td>1/50</td>
<td>17/50</td>
<td>24/50</td>
<td>7/50</td>
<td>26/50</td>
<td>35/50</td>
</tr>
</tbody>
</table>

No clinical observations attributable to substance administration were reported in any of the treated groups. Although statistically significant differences in mean food consumption were occasionally noted in the treated groups relative to the controls, these differences occurred sporadically and there was no dose-effect relationship. Water consumption of the treated groups was similar to that of the controls at the 18 and 24 month intervals.

During the intermediate months of this study, the mean body weights of the treated animals were slightly lower than the controls. The maximum body weight reductions for males ranged from 6% in the high-dose group to 2-3% in the low-dose group. For females these differences were statistically significant only during months 20 and 21 and they were not dose-related. From month 24 until study termination the mean body weights of all treated groups were comparable to the controls.

Haematology, blood biochemistry and urinalysis parameters deviated occasionally and some of them were statistically significantly different from controls. These differences were not dose-related and not consistent over time or between sexes.

No statistically significant differences were noted in the terminal absolute and relative organ weights of the treated groups when compared to the controls. The few inter-group differences were not dose-related nor consistent.

Gross observations at necropsy were similar in incidence between treatment groups and controls of both sexes. These lesions consisted primarily of inflammatory and structural changes that are commonly found in rats of this strain in lifetime studies.

The incidence and severity of the microscopic lesions were similar between the treatment groups and controls of both sexes. The most frequently observed changes occurred in the lungs and the kidneys, and were associated with chronic respiratory disease and chronic progressive nephropathy. Both lesions are a common age-related disease in this strain of rats.
A slightly elevated incidence was noted for lymphocytic hyperplasia in the thymus and the lymph nodes when compared to controls. This lesion is known to occur spontaneously in older rats and is quite variable in the thymus. In contrast, the incidence of this lesion was not elevated in the spleen, a more reliable indicator of lymphocytic hyperplasia. The severity of this lesion was similar for treated and control rats (minimal to moderate). Moreover, there was no clear dose-effect relationship and there were no corroborating changes of haematologic parameters.

A variety of neoplasms was found in both control and treated animals. The most common tumours were found in the pituitary of both sexes and in the mammary glands of the females. The incidence of all tumour bearing animals in the treated groups and the controls were similar and did not exhibit any dose-effect relationship. The incidence of interstitial cell tumours in the testes was increased in the treated animals when compared to the controls (15% at the highest dose at terminal sacrifice). This effect was not related to compound administration since the incidence of this tumour is known to vary a lot and the incidences observed in the treated groups remained well within the historical range of this laboratory (6-27% at terminal sacrifice). Beside, the incidence in the control group was unusually low (0%) for this type of tumour.

Conclusion: Lifetime administration of glyphosate acid to rats via the diet did not cause any adverse chronic toxicity or carcinogenic effect at any of the dose levels tested. On the basis of these study results the no-effect level for chronic toxicity and carcinogenicity is 31.5 and 34.0 mg/kg bw/day, the highest dose tested for males and females, respectively.


Deviations: Although this study was conducted prior to the publication of Directive 87/302/EEC for carcinogenicity tests, the protocol generally adhered to this guideline. The only discrepancy was that sternum with bone marrow was not evaluated histopathologically. This minor discrepancy is not considered to have affected the scientific validity of this study and it is considered appropriate for determining the oncogenic potential of glyphosate in mice.

GLP: This study was conducted prior to the establishment of GLP requirements. However, the report received a quality assurance review by Bio/dynamics Inc. to assure conformance with the study protocol and the raw data.

Materials and methods: Glyphosate (purity 99.7%) was fed ad libitum to four groups of 50 male and 50 female Charles River CD-1, mice for 24 months at dietary levels of 0, 1,000, 5,000 and 30,000 ppm. Diet analyses to confirm the stability of glyphosate, its homogeneity in the diet and the accuracy of the intended concentrations are presented in a separate report (BD-77-420A).

All animals were observed twice daily for mortality and clinical signs of toxicity. Body weights and food consumption were determined pre-test, weekly through 14 weeks and every two weeks for the remainder of the study. Feed efficiencies were calculated once pre-test and weekly through 14 weeks. Water consumption was measured for 10 animals/sex/group at month 12 and for 12 animals/sex/group at month 24.

Blood samples were taken from 10 animals/sex/group at months 12 and 18 for haematologic evaluations. At month 24, samples were taken from 12 males/group and from all surviving females. The haematology parameters measured were total erythrocyte count, total leukocyte count, platelet count, hematocrit, haemoglobin, leukocyte differential formula and erythrocyte morphology.

Brain, adrenals, kidneys, liver, heart, ovaries, spleen and testes were weighed.

Complete gross necropsy examinations were performed on all animals which died, were killed in extremis or were sacrificed at study termination. The tissues preserved for histopathology were aorta, adrenals, bone and bone marrow, brain, caecum, colon, duodenum, oesophagus, eyes, Harderian gland, gonads, heart, ileum, jejunum, kidneys, liver, lung, mammary gland, lymph nodes, muscle, pancreas, pituitary, prostate, nerve, skin, spleen, stomach, mandibular salivary gland, tissues with lesions and/or masses, thymus, thyroid/parathyroid, uterus and urinary bladder. In addition, the spinal cord (cervical and thoracolumbar) and 3 coronal sections of the head (including nasal cavity, paranasal sinus, tongue, oral cavity, nasopharynx and middle ear) were examined for 10 animals/sex/group.
Findings: Analysis of treated diets demonstrated that glyphosate could be homogeneously mixed with rodent diet and that it remained stable in the diet for the one week feeding period used in this study. Glyphosate test concentrations averaged approximately 95% of the target concentrations throughout the study. Compound intake, expressed as mg glyphosate/kg bw/day on a time-weighted average, was 157, 814 and 4841 mg/kg/day for males and 190, 955 and 5874 mg/kg/day for females at the low-, mid- and high-dosage levels, respectively.

The incidence of mortality in all groups was normal for this age and strain of mice (table 1).

Table 1. Cumulative mortality of mice from all groups

<table>
<thead>
<tr>
<th>Concentration in diet (ppm)</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9/50</td>
<td>12/50</td>
<td>30/50</td>
<td>3/50</td>
<td>15/50</td>
<td>30/50</td>
</tr>
<tr>
<td>1,000</td>
<td>9/50</td>
<td>19/50</td>
<td>34/50</td>
<td>4/50</td>
<td>16/50</td>
<td>38/50</td>
</tr>
<tr>
<td>5,000</td>
<td>7/50</td>
<td>14/50</td>
<td>33/50</td>
<td>1/50</td>
<td>8/50</td>
<td>23/50</td>
</tr>
<tr>
<td>30,000</td>
<td>4/50</td>
<td>11/50</td>
<td>24/50</td>
<td>5/50</td>
<td>13/50</td>
<td>27/50</td>
</tr>
</tbody>
</table>

There were no physical or behavioural signs of toxicity which were considered to be related to glyphosate administration. Observations such as yellow staining of the anogenital area, alopecia (hair loss) and lacrimation were noted with approximately equal frequency in both control and treated animals and are considered common for the CD-1 mouse under laboratory conditions.

Body weights for both males and females of the high-dose group were consistently less than controls throughout the study. Although the decreases were slight (1% to 11%), several were statistically significant. Other statistically significant decreases were also noted in the mid- and low-dose animals; however, these changes were sporadic and did not reflect a dose-response relationship. Food consumption and feed efficiency values for all groups, including controls, were extremely variable, which is a common finding with mice. No consistent differences between treated animals and controls were demonstrated. Also no treatment-related effects were observed for water consumption.

Several statistically significant differences from controls were observed for some of the haematology parameters examined. However, the changes were small in magnitude, inconsistent over time, and did not occur in a dose-related pattern. None were considered related to test-material administration.

There were no changes observed in the absolute or relative organ weights which were considered to be due to glyphosate administration. Several statistically significant changes in organ/body weight ratios were observed, but these were attributed to the statistically significant decreases in terminal (fasted) body weights rather than a specific organ effect. There were no dose-response relationships or any correlated gross or microscopic observations in any of the organs.
At terminal necropsy, frequent gross observations included ovarian and uterine cysts in females and such minor observations as scabbed and torn skin and truncated tails in both males and females. All these findings were observed with approximately equal frequency in all dose groups and controls. Other gross findings were low in incidence, considered to be typical for mice of this age and were unrelated to glyphosate administration.

The incidences of neoplastic and non-neoplastic lesions were analysed by the Cochran-Armitage test for linear trend and the Chi-Square test (uncorrected for continuity) for treatment group differences from control.

Statistically significant positive trends were observed for central lobular hepatocyte hypertrophy, centrilobular hepatocyte necrosis and chronic interstitial nephritis in males, and for proximal tubule epithelial basophilia and hypertrophy in females. Statistically significant increases in the incidence of lesions in treatment groups vs. control were observed for centrilobular hepatocyte necrosis in high-dose males and proximal tubule epithelial basophilia and hypertrophy in high-dose females. Regarding the kidney findings, while the incidences and/or dose response trends of these individual microscopic kidney lesions were found to be statistically significant, they are considered to be part of a spectrum of lesions which, as a whole, constitute spontaneous renal disease. Thus, no one component should be singled out as evidence of compound related kidney damage. When the entire spectrum of kidney findings observed in this study are examined, no evidence is found of a treatment-related effect. The lesions which were considered to be possibly related to glyphosate treatment are hepatocyte hypertrophy and centrilobular hepatocyte necrosis in high-dose males. Both these findings, however, are of the type and severity common to long term mouse studies. The incidences of these lesions are shown in table 2.

Table 2. Incidences of hepatocellular lesions in all mice

<table>
<thead>
<tr>
<th>Sex</th>
<th>Concentration in the diet (ppm)</th>
<th>0</th>
<th>1000</th>
<th>5000</th>
<th>30,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centrilobular hypertrophy</td>
<td>M</td>
<td>9/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5/50</td>
<td>3/50</td>
<td>17/50</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0/49</td>
<td>5/50</td>
<td>1/49</td>
<td>1/49</td>
</tr>
<tr>
<td>Centrilobular necrosis</td>
<td>M</td>
<td>0/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2/50</td>
<td>2/50</td>
<td>10/50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
<sup>a</sup> Statistically significant linear trend (p≤0.01) using the Cochran-Armitage test

The incidences of urinary bladder hyperplasia in males were 3/49, 3/50, 10/50 and 8/50. It was concluded that the higher incidences at the mid and high dose were not treatment-related because there was no statistical significance and there was no true dose-related trend.

There were no statistically significant increases in the incidence of neoplastic lesions in treatment groups vs. control. There were also no statistically significant positive trends observed. The majority of the neoplastic findings were bronchiolar-alveolar tumours, hepatocellular tumours and tumours of the lymphoreticular system. The incidences of these tumours, however, were small and they are all of the type commonly encountered in
mice. No treatment relationship was suspected. The incidence of renal tubule adenomas was 1/49, 0/49, 1/50 and 3/50 in control through high-dose males, respectively. This lesion, however, was not observed in any of the female treatment groups and, as mentioned previously, the incidence of renal tumours in the high-dose group was not statistically different from the controls and there was no statistically significant dose-response trend. The slightly increased incidence of adenomas in the high-dose males was considered to be spurious and unrelated to glyphosate administration.

The correlation of microscopic findings with gross necropsy observations did not reveal evidence of any treatment-related effects.

**Conclusion:** The oral administration of glyphosate to mice at concentrations up to 30,000 ppm in the diet for 24 months resulted in slightly reduced body weight gain in high-dose males and females and several microscopic liver changes in high-dose males possibly related to test material administration. No changes in food consumption, clinical or gross necropsy observations and clinical chemistry parameters were noted, and no neoplasms considered to be related to glyphosate administration were observed. The oncogenic no-effect level was considered to be 30,000 ppm. The chronic toxicity NOEL was established at 5,000 ppm in the diet (814 mg/kg bw/day and 955 mg/kg bw/day for males and females, respectively).
Materials and methods: Glyphosate acid (96.13% w/w) was administered orally in gelatin capsules to three groups of six male and six female Beagle dogs at daily doses of 0, 20, 100 and 500 mg/kg/bw for one year. The high dose level was selected based upon the maximum size and number of capsules which could reasonably be administered daily to a dog for one year. Control groups received empty gelatin capsules.

All animals were observed at least twice daily for mortality and signs of toxicity. Body weights and food consumption were recorded weekly. Ophthalmologic examinations were performed on each dog pre-test and at study termination.

Blood samples were collected pre-test and at months 3, 6 and 12 of the study. The haematology parameters measured were total erythrocyte count, total leukocyte count, platelet count, haematocrit, haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, leukocyte differential formula, reticulocyte count and prothrombin time. The blood biochemistry parameters measured were albumin, globulin, total protein, blood urea nitrogen, total bilirubin, direct bilirubin, glucose, transaminases (ALT and AST), alkaline phosphatase, γ-glutamyl transferase, creatinine, cholesterol, calcium, phosphorus, sodium and potassium.

At months 3, 6 and 12 of the study urine was collected from each animal. The parameters determined in urine were bilirubin, blood, glucose, ketones, pH, protein, urobilinogen, specific gravity, appearance and opacity. Urine sediment samples from each animal were analysed for bacteria, epithelial cells, erythrocytes, leukocytes, casts or abnormal crystals if there was evidence of abnormal amounts of blood or protein in the urine.

At termination of the study, all animals were sacrificed and given a complete gross necropsy examination. The following organs were weighed: adrenals, brain, heart, kidneys, liver, ovaries, pituitary, testes with epididymides, thyroid/parathyroid.
The tissues preserved for histopathology were aorta, adrenals, rib with marrow, brain, caecum, colon, duodenum, oesophagus, eyes with optic nerves, gall bladder, heart, ileum, jejunum, kidneys, liver, lung, lymph nodes (mesenteric), mammary gland, muscle, ovaries, pancreas, pituitary, prostate, rectum, sciatic nerve, skin, spinal cord, spleen, stomach, mandibular salivary gland, testes with epididymides, thymus, thyroid/parathyroid, tissues with lesions and/or abnormal masses, trachea, ureter, uterus and urinary bladder.

**Findings:** All dogs survived until study termination. Body weights and food consumption were similar between all treated and control groups for both sexes throughout the study. There were no clinical observations reported which were considered to be treatment related. No ocular abnormalities were noted at either the pre-or post-exposure evaluation periods. No treatment-related alterations in haematologic parameters were observed. There were no treatment-related urine abnormalities detected. There were no significant differences in terminal body weights or in the incidence of gross lesions for either sex when control and treated groups were compared. Absolute pituitary weights of mid and high dose males were significantly lower than control values. Since no microscopic abnormalities were noted in the pituitaries of these dogs, no dose-trend relationship was observed, and as pituitary weights can be quite variable, the observed decreases could not be conclusively attributed to glyphosate administration. Absolute brain weights for mid dose males were slightly lower than in the control group. However, since the brain weights in the low and high dose levels were comparable to controls, this effect was not considered to be treatment-related. Organ to body weight ratios were similar for control and treated animals of both sexes. There were no microscopic lesions that could be associated with administration of glyphosate.

**Conclusion:** There were no treatment-related effects noted when glyphosate was orally administered to dogs at levels of 20, 100 and 500 mg/kg/day for one year. The no-effect level for chronic toxicity in the dog is considered to be 500 mg/kg/day, the highest dose tested.
Materials and methods: Glyphosate (96.5% pure) was administered in the diet to four groups of 60 male and 60 female Charles River CD (SD) BR rats at target concentrations of 0, 2,000, 8,000, and 20,000 ppm for 24 months. The highest dose of 20,000 ppm (approximately 1000 mg/kg) is considered to be a limit test for chronic/oncogenicity studies.

Food and water were provided ad libitum. Fresh diets were prepared at approximately weekly intervals. Samples of these diets were routinely analysed to verify dietary concentrations. Analyses to verify homogeneity of the diet mixtures were performed twice during the study. The stability of the diet mixture was analysed once. The stability of the neat test material was determined prior to the study start, during months 8, 14, 21, and after the in-life portion of the study.

All animals were observed twice daily for mortality and moribundity. Detailed observations for clinical signs of toxicity were performed weekly. Body weights and food consumption were determined each week for the first 13 weeks and then every fourth week thereafter. Ophthalmic examinations were performed at pre-test and just prior to terminal sacrifice.

Haematology, blood biochemistry and urinalysis determinations were conducted on 10 animals/sex/dose each at months 6, 12 (interim sacrifice), 18, and 24 (study termination). The haematology parameters measured were total erythrocyte count, total leukocyte count, platelet count, hematocrit, hemoglobin, mean corpuscular volume, mean
corpuscular hemoglobin, mean corpuscular hemoglobin concentration, leukocyte differential formula and reticulocyte count. The blood biochemistry parameters measured were albumin, globulin, total protein, blood urea nitrogen, total bilirubin, direct bilirubin, glucose, transaminases, alkaline phosphatase, creatinine, cholesterol, calcium, phosphorus, chloride, sodium and potassium. The parameters determined in urine were bilirubin, blood, glucose, ketone, pH, protein, urobilinogen, specific gravity, appearance and microscopic examination when excess blood or protein present.

Ten animals/sex/dose were sacrificed at month 12, and all survivors were sacrificed at month 24. All animals were given a complete gross necropsy. Brain, kidneys, liver and testes with epididymides were weighed. Approximately 40 tissues were preserved and examined microscopically. The tissues preserved for histopathology were aorta, adrenals, bone and bone marrow, brain, caecum, colon, duodenum, oesophagus, eyes, Harderian gland, heart, ileum, jejunum, kidneys, tissues with lesions and/or abnormal masses, liver, lung (with mainstem bronchi), lymph nodes (mesenteric and submandibular), muscle (quadriceps femoris), ovaries, nasal turbinates, pancreas, pituitary, prostate, rectum, sciatic nerve, seminal vesicles, skin (with mammary tissue), spinal cord (cervical, thorax, lumbar), spleen, stomach, submaxillary salivary gland, testes with epididymides, thymus, thyroid/parathyroid, trachea, uterus (corpus and cervix) and urinary bladder.

**Findings:** Stability analyses indicated that the neat test material was stable throughout the study. The stability and homogeneity of the diet mixtures were determined to be adequate. Analyses to verify dietary concentrations demonstrated that average glyphosate concentrations were 95% of target levels for all dose groups.

There were no statistically significant differences in group survival rates. At the end of the study, the percentages of animals surviving at 0, 2,000, 8,000, and 20,000 ppm were 29, 38, 34, and 34 for males, respectively, and 44, 44, 34, and 36 for females.

Various clinical signs were noted throughout the study. However, they were typical of those frequently observed in chronic studies and appeared to be randomly distributed in all groups. Therefore, none were considered to be related to administration of the test material.

Statistically significant reductions in body weight were noted in high dose females from week 7 through approximately the twentieth month. During this time, absolute body weights gradually decreased to 14% below the control value. Body weight gain in high dose females was also consistently reduced compared to control. At the point of maximum body weight depression (20 months), cumulative body weight gain was 23% less than control. Body weight gain in all treated male groups was comparable to controls.

There were no statistically significant decreases in food consumption in either sex at any time in the study; significant increases were noted frequently in high dose males. Overall study averages for consumption of test material (mg/kg) were 89, 362, and 940 in males and 113, 457, and 1,183 in females for the low, mid, and high dose groups, respectively.
The ophthalmic examination prior to study termination revealed a statistically significant difference (p<0.05) between the incidences of control and high level males displaying cataractous lens changes (0/15 vs. 5/20). This incidence (25%) was within the range (0 to 33%) observed in previously conducted studies at this laboratory with male CD rats. The incidences of cataractous lens changes in low and mid dose males, as well as all treated female groups, were comparable to their respective controls. Dr. Rubin's examination, which provided a second opinion, also revealed a statistically significant increase (p<0.05) in cataractous lens changes in high dose male animals (1/14 vs. 8/19). Dr. Rubin concluded that there appeared to be a treatment-related occurrence of lens changes affecting high dose males. Histopathological examination of the eyes by the Monsanto histopathologist revealed the incidences of cataract and/or lens fibre degeneration as shown in Table 1.

<table>
<thead>
<tr>
<th>Dose (ppm in diet)</th>
<th>0</th>
<th>2,000</th>
<th>8,000</th>
<th>20,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal sacrifice</td>
<td>2/14</td>
<td>3/19</td>
<td>3/17</td>
<td>5/17</td>
</tr>
<tr>
<td>All animals</td>
<td>4/60</td>
<td>6/60</td>
<td>5/60</td>
<td>8/60</td>
</tr>
</tbody>
</table>

None of the incidences in the treatment groups are significantly different from control. However, it is difficult to distinguish between mild cataractous lens changes and postmortem autolysis during routine histopathological examination of the lens. Therefore, slides of all eyes from each group were submitted to Environmental Pathology Laboratories for a second evaluation which found 3, 4, 4, and 8 males with degenerative lens changes (excludes autolytic changes) in the control, low, mid and high dose groups, respectively. It was concluded that there was an increased incidence (not statistically significant) of basophilic degeneration of the posterior subcapsular lens fibers in the high dose males, but not in mid or low dose males, nor any treated female group.

To summarize, ophthalmic examinations performed at the end of the study revealed a statistically significant increase in the incidence of degenerative lens changes in high dose males; however, the incidence was within the historical control range. Histopathological examination also indicated a slightly increased incidence of degenerative lens changes in high dose males, although the difference was not statistically significant. Interpretation of these data are difficult since the numbers of animals examined ophthalmologically and affected at the end of the study were small. Nonetheless, the occurrence of degenerative lens changes in high dose male rats appears to have been exacerbated by treatment. There is no indication of treatment-related ocular effects in low or mid dose males or in any group of treated females.

There were various changes in haematology and serum chemistry parameters. However, the changes were not consistently noted at more than one timepoint, were within historical control ranges, small in magnitude, and/or did not occur in a dose-related manner. Therefore, they were considered to be either unrelated to treatment or toxicologically insignificant.
There was a statistically significant increase in urine specific gravity in high dose males at the 6 months. Statistically significant reductions in urine pH were also noted in high dose males at months 6, 18, and 24. This may have been related to the renal excretion of glyphosate which is a weak acid.

The following statistically significant increases in liver weight were noted in high dose males: liver-to-body weight ratio at 12 months, absolute liver weight and liver-to-brain weight ratio at 24 months. There were no other statistically significant changes in organ weights which occurred in a dose-related manner. Gross abnormalities observed at necropsy were not considered related to glyphosate administration.

Histopathological examination revealed an increase in the number of mid dose females displaying inflammation of the stomach squamous mucosa. This was the only statistically significant occurrence of non-neoplastic lesions. The incidences of this lesion in all groups of animals are shown in table 2.

Table 2: Incidence of inflammation of the stomach squamous mucosa in the rat

<table>
<thead>
<tr>
<th>Concentration in the diet (ppm)</th>
<th>0</th>
<th>2,000</th>
<th>8,000</th>
<th>20,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>2/58</td>
<td>3/58</td>
<td>5/59</td>
<td>7/59</td>
</tr>
<tr>
<td>Females</td>
<td>0/59</td>
<td>3/60</td>
<td>9/60</td>
<td>6/59</td>
</tr>
</tbody>
</table>

Although the incidence (15%) of this lesion in mid dose females was slightly outside the historical control range (0 to 13.3%) for the laboratory, there was no dose-related trend across all groups of treated females and there was no significant difference in any male group. Therefore, the finding was not considered treatment related. The only statistically significant difference in neoplastic lesions between control and treated animals was an increase in the number of low dose males with pancreatic islet cell adenomas. The incidences of this lesion were 1/58 (2%), 8/57 (14%), 5/60 (8%), and 7/59 (12%) in control, low, mid, and high dose group males, respectively. The historical control range for this tumor at the testing laboratory (EHL) is 1.8 to 8.5%, but a partial review of studies reported recently in the literature revealed a prevalence of 0 to 17% in control males with several values greater than or equal to 8%. The incidences of islet cell adenomas clearly did not follow a dose-related trend in the treated male groups as indicated by the lack of statistical significance in the Peto trend test. This indicates that the distribution of incidences in the four groups was random. It should be noted that there was also considerable inter-group variability in the numbers of females with this tumour (5/60, 1/60, 4/60 and 0/59 in the control, low, mid and high dose groups, respectively). There was no evidence of dose-related pancreatic damage or pre-neoplastic lesions. The only pancreatic islet cell carcinoma found in this study occurred in a control male, thus indicating a lack of treatment-induced neoplastic progression. Taken together, the data support a conclusion that the occurrence of pancreatic islet cell adenomas in male rats was spontaneous in origin and unrelated to glyphosate administration.
Conclusion: Dietary administration of glyphosate to male and female Sprague-Dawley rats for 2 years resulted in toxicologically significant reductions in female body weight gain and cataractous lens changes in males at 20,000 ppm. The chronic NOAEL is considered to be 8,000 ppm for both sexes. Glyphosate did not produce an oncogenic response in this study.