[redacted]

AUTHENTICATION OF AMENDMENT TO FINAL REPORT

Glyphosate Technical:

DIETARY CARCINOGENICITY STUDY IN THE MOUSE

PROJECT NUMBER: 2060-0011

REASON FOR AMENDMENT

1. Clarification of histopathological finding for Testis on page 41 of the final report.
2. Correction of typographical errors on pages 705 and 896.

DETAILS OF AMENDMENT

Report pages 41-45 - Section 5.11.3.

The report page has been amended to include further statements to clarify the finding of testicular atrophy as follows:

Page 705, Appendix 9 - Animal Number 5. The reporting of atrophy Testis 1 (minimal) has been added to the report to reflect raw data and statistical analysis.

Page 896, Appendix 9 - Animal Number 171. The reporting of Testis 2 atrophy (marked) has been amended due to a typographical error of reporting Testis 1 on two occasions.

This amendment does not affect the validity or interpretation of the data.

[redacted] ..... DATE: 12 May 2011

Study Director

This amendment has been audited by [redacted] Quality Assurance Unit and is considered to be an accurate account of the project.

[redacted] ..... DATE: 13 MAY 2011

For the Quality Assurance Unit*

***Authorised QA Signatures:**
Senior Audit Staff: [redacted]

TESTIS: Interstitial (Leydig) cell hyperplasia of the testis was seen in the majority of animals examined and is a common testicular change in ageing male mice. The group distribution of incidence or severity was not influenced by treatment with the test material. Testicular atrophy, unilateral or bilateral, is also an anticipated condition in the senescent mouse and again there was no influence of treatment on the group distribution of incidence or severity. The incidence of bilateral testicular atrophy did attain statistical significance for high dose animals ($P < 0.05$) but this was considered to be of no toxicological significance.

A statistical significance was seen for the incidence of testicular atrophy (irrespective of severity grade) for "Testis 2" at 5000 ppm Glyphosate technical compared with controls at terminal kill only. A similar finding was not observed for a similar assessment for "Testis 1". The following will clarify the observation and provide rationale for a further analysis of the data:

Clarification of the term Testis 1 and Testis 2. At macroscopic *post mortem* examination of animals at both interim (decedent) and study termination (terminal kill) necropsy, the dissected tissues were weighed and/or preserved in fixative for subsequent histology and histopathological examination: The method of tissue preservation and histological preparation of the testes was as follows:

i. Both testes were preserved in the same tissue sample pot. No attempt was made to differentiate the origin of each testis from the left or right side of the body.

ii) At histological preparation, both testes were embedded in the same wax block. The positioning of each testis (from either left or right side of the animals body) within the block was entirely random.

iii) Subsequent slide production from wax blocks produced samples of sections of both testes but with no indication from what side of the body they were derived.

Histopathological examination of slides of testes therefore, was conducted in a standard fashion. Lack of knowledge of origin of location of each testis (either right or left side of the body) has meant that the pathologist randomly assigned the terminology.

Testis 1 First testis on slide examined.
Testis 2 Second testis examined.

As a consequence of this randomised approach in the preparation and examination of this paired organ (testis) there occurred a random and entirely fortuitous difference in incidence of testicular atrophy in Testis 2 for treated animals compared with controls but not a similar finding for Testis 1.

Since there is no distinguishable difference between the tissue samples attributed the label "testis 1" from those labelled "testis 2" then clearly the only way to analyse the incidence of lesions found within these tissues is to treat them as a single source and combine the incidence.

The following table shows the incidence of unilateral or bilateral testicular atrophy of mice in the control and high dose group. Where a mouse had different grades of lesion in each testis, it is included in the more severe of the categories. The data has been checked to ensure that an individual mouse only appears once in the table below. (When treated unilaterally, a mouse with bilateral atrophy would appear in both testis 1 and testis 2).

Table 2 Distribution of severity grades for testicular atrophy (unilateral/bilateral).

Severity Grade*	Incidence of unilateral or bilateral testicular atrophy	
	Control (0 ppm)	High Dose (5000 ppm)
Total examined	39	35
Absent	15	18
Minimal	13	8
Slight	4	3
Moderate	1	1
Marked	4	4
Severe	2	1
Total affected (regardless of grade)	24	17

* for bilateral atrophy - maximum severity grade counted

The distribution of severity grades for combined testis results show no significant trend towards increased severity of the finding. In addition the majority of affected animals were for minimal severity only. Due to the clear lack of any effect, no statistical analysis of this data has been performed.

Spermatocoel formation, focal mineralisation of tubules, focal hyperplasia of the rete tubular epithelium and non-neoplastic cyst formation were incidental changes observed occasionally or rarely and considered to be of no toxicological significance.

Benign interstitial (Leydig) cell tumours were seen in two control mice.

EPIDIDYMIS: Reduced spermatozoal content, spermatocoel and spermatocoel granuloma formation, eosinophilic contents, interstitial mononuclear cells and fibrosis, and distension of ducts were all observed with low incidences and as age-related changes. There was no indication of an effect of treatment on epididymal pathology and no epididymal tumours were seen.

PREPUTIAL GLAND: Samples of preputial gland were included incidentally with sections of inguinal or peri-genital skin/subcutis that were sampled with lesions reported clinically or at necropsy, and thus are not available for all male animals. Inflammatory and atrophic lesions of the preputial gland are common in ageing male mice were seen in samples of preputial gland in this investigation. Abscess formation was seen occasionally and an instance of keratin cyst formation was also reported. There was no effect of treatment on preputial gland pathology, and neoplasia of the preputial gland was not seen.

PROSTATE: Focal epithelial hyperplastic and atrophic changes are commonly seen in the prostate gland of ageing mice and there was a relatively high incidence of such conditions among control and treated mice in this study with no relationship to treatment. Mononuclear cell foci, mixed inflammatory cell infiltrates, interstitial fibrosis, and abscess formation were encountered occasionally or rarely as spontaneous changes and there were no neoplastic lesions.

SEMINAL VESICLES: Variations in secretory content of the seminal vesicles are common in rodents and are exacerbated by age. Because of the largely subjective nature of the assessment of size in histological sections and since distension may be lost if fluid leaks from the vesicles during sampling and fixation, only appreciable differences in secretory content were estimated histopathologically in this study. For these reasons there was not always a good correlation between necropsy observations and histopathological findings for this parameter.

Cystic distension of one or both vesicles was encountered frequently and there was no difference in the incidence of the condition between control and high dose groups. A reduced secretory content of the vesicles was seen occasionally and the incidence of this similarly had no relationship to treatment. Focal hyperplasia of the epithelial lining of the vesicles, mononuclear cell foci, mixed inflammatory cell infiltrates, fibrous thickening, atrophy, and abscess formation were also observed occasionally or rarely and without a treatment association. Hyperplasia of the coagulating gland was seen for one high dose animal.

An adenoma of the vesicular epithelium was seen for two control mice and a leiomyosarcoma was observed in a high dose animal, the latter being unrelated to treatment.

REPRODUCTIVE TRACT (FEMALE): Atrophic changes are frequently encountered in the ovaries and uterus of senescent female mice and are regarded as part of the normal morphology in these animals.

OVARY: Ovarian cysts are common in ageing female mice and usually arise either from follicular elements or from the bursa or immediately proximal elements of the oviduct. A distinction was made between follicular cysts and those of non-follicular origin, and although many samples were not sectioned such as to allow the precise origin of non-follicular cysts to be determined, most could be attributable to distension of the bursa. Such changes were encountered in the majority of animals examined and the group distribution of incidence was unrelated to treatment. Cystic and haemorrhagic follicles or corpora lutea were observed in several control and high dose animals and the incidence was unrelated to treatment. Interstitial cell hyperplasia, vasculitis, rete cyst formation, cystic distension of the oviducts, non-neoplastic haemorrhagic cyst formation, and necrosis and interstitial haemorrhage were also seen occasionally or rarely and without treatment association. Necrosis of adjacent ovarian adipose tissue was seen in one low dose female.

Ovarian tumours were encountered in nine animals. Although five of these occurred among high dose group mice compared with one in the control group, the diversity of tumour type did not suggest an effect of treatment on ovarian neoplasia.

UTERUS: Cystic endometrial hyperplasia was seen in the majority of mice examined. This is a common age-related condition in laboratory maintained female mice and neither the incidence nor severity of the condition was related to treatment in this investigation. Uterine atrophy is also a common senescent change and was similarly unrelated to treatment. Occasional or rare instances of vasculitis, lymphoid foci, haemorrhagic cyst formation, and angiectasis were also seen and were not influenced by treatment.

Uterine tumours were seen in twenty mice, the group distribution of which was unrelated to treatment. Six uterine tumour types were diagnosed, the most frequently observed being endometrial stromal polyp which accounted for just over half of the reported uterine neoplasms. The group incidence of endometrial stromal polyp was not related to treatment.

Histiocytic sarcomas were observed to originate in the uterus of five animals. Histiocytic sarcoma is considered above under lymph nodes and thymus.

VAGINA: Epithelial keratinisation was seen as a normal cyclical change in the mouse vagina and an isolated instance of peripheral lymphocyte infiltration was reported. There were no treatment-related changes in the vagina and no neoplastic conditions were observed.

SALIVARY GLANDS: Submandibular, sublingual, and parotid salivary glands were examined. Secretory depletion of the submandibular gland was observed frequently and was more prevalent in female than in male mice. There was no treatment-related distribution of incidence or severity of secretory depletion. Isolated instances of lymphocyte infiltration, distension of ducts, atrophy, abscess formation, hypertrophy of mucous acini, and peripheral inflammation were also seen as spontaneous conditions that were unrelated to treatment. There were no neoplastic salivary gland lesions.

SKELETAL MUSCLE: No significant skeletal muscle pathology was encountered. Isolated instances of mononuclear cell foci, vasculitis, and focal mineralisation were observed as spontaneous changes. No neoplastic conditions were seen in the skeletal muscle.

SKIN/SUBCUTIS: In addition to routine samples of skin and subcutaneous tissue, further samples were taken from macroscopically observed lesions. There were no treatment-related conditions seen in the skin or in subcutaneous tissues, but several spontaneous lesions were observed. Epidermal ulceration and scab formation, inflammatory lesions, abscess formation, focal acanthosis, focal mineralisation, focal dermal thickening, and focal necrosis were seen occasionally or rarely and without significance. A few instances of ectasia, atrophy, or inflammation of unidentified subcutaneous glandular tissue were also observed and these lesions were similarly not related to treatment.

Dermal/subcutaneous fibrosarcoma was seen in six male mice and although none of these occurred among control animals there was no suggestion of a treatment-related group distribution of incidence. A haemangiosarcoma was seen in one low dose female mouse.

SPLEEN: Higher grades of severity of extramedullary haemopoiesis in the spleen, usually secondary to significant pathology elsewhere, were observed relatively frequently in mice of either sex and there was no treatment-related group distribution of incidence. Lymphoid hyperplasia, atrophy of lymphoid tissue, and atrophy of the red pulp were also seen as background spontaneous changes with no indication of an influence of treatment upon incidence or severity.

Haemagiomatous neoplasms were seen in three mice; a haemangioma was seen in one control male mouse with haemangiosarcomas in one control female and in one high dose group female. There was no effect of treatment on the development of neoplasia in the spleen. The spleen was a frequent site for multicentric development of lymphoma discussed above under lymph nodes and thymus.

STOMACH: Mucosal hyperplasia is commonly observed as an age-related change in laboratory maintained mice and such was the case in this study. There was no appreciable difference in prevalence between the sexes and the group distribution of incidence or severity demonstrated there to be no effect of treatment. Acanthosis and hyperkeratosis of the forestomach were also seen frequently for either sex and were similarly of no toxicological significance. Subepithelial, and mucosal and submucosal inflammation, epithelial ulceration, mineralisation of the muscularis, diverticulum formation, and focal mucosal necrosis were seen occasionally or rarely as

spontaneous conditions none of which was attributable to treatment. Gastric neoplasia was not observed in any mice in this investigation.

THYROID/PARATHYROID GLANDS: There were no treatment-related effects in the thyroid gland. A few spontaneous conditions were seen occasionally or rarely and included distension and coalescence of follicles, focal follicular cell hyperplasia, focal C-cell hyperplasia, vasculitis, focal inflammation, follicular cell hypertrophy, and mononuclear cell foci. Thyroid tumours were not observed in mice in this investigation

Isolated instances of focal hyperplasia and mononuclear cell foci were seen in the parathyroid glands and there were no parathyroid tumours.

TONGUE: Focal inflammation, fibrosis, ulceration, vasculitis, and abscess formation were observed occasionally or rarely. There were no treatment-related changes and no neoplastic conditions were seen.

UPPER RESPIRATORY SYSTEM: Very few pathological changes were seen in the pharynx, larynx, or trachea.

PHARYNX: Pharyngeal pathology was present in only a few animals and included mononuclear cell infiltrates, exudate overlying the epithelium, and focal epithelial hyperplasia, none of which was related to treatment. Extensive inflammation and abscess formation in the supra-pharyngeal tissues and extending into the brain for a control male mouse was an unusual spontaneous lesion.

LARYNX: Incidental laryngeal changes included dilatation of subepithelial glands and epithelial and/or subepithelial inflammatory cell infiltrates none of which was related to treatment.

TRACHEA: Dilatation of subepithelial glands was observed frequently in both sexes and there was no evidence of a treatment-related group distribution of incidence. Isolated instances of inflammation were also seen and were unrelated to treatment.

No neoplastic lesions were seen in the pharynx, larynx or trachea.

TISSUE MASSES and OTHER ORGANS: Masses and other lesions observed clinically or at necropsy were sampled and examined histopathologically. The pathology for these was usually reported under the specific tissue such as skin/subcutis or mammary gland to ensure that all conditions for these tissues were accurately summarised and analysed. Other non-protocol tissues were sampled occasionally as lesions observed macroscopically:

ABDOMINAL MASS: A nodule of fat necrosis and keratin cyst formation were encountered among low dose group male mice. A lipoma was seen for one control female mouse and a mesothelioma and an anaplastic sarcoma were seen in each of two high dose male mice. These latter neoplasms were considered to be unrelated to treatment.

CERVICAL MASS: Extensive abscess formation was reported in the cervical tissues of one intermediate dose male mouse.

HIND LIMB: Subcutaneous and periosteal inflammation with abscess formation was observed in a low dose group male mouse

TAIL: A subcutaneous keratin cyst was seen in a few mice of either sex. Isolated instances of focal hyperostosis of bone, focal acanthosis and hyperkeratosis, and focal inflammation were also reported. None of these conditions was related to treatment with the test material.

GLYPHOSATE TECHNICAL : DIETARY CARCINOGENICITY STUDY IN THE MOUSE

Appendix 9 (continued) Individual Clinical and Pathological Findings

Animal Number: 5

Dose Level: 0 (control) Sex: Male

Day of Death: 558 Fate: Terminal kill

Clinical Findings	Day of Observations (Onset - Completion)
Mass	248 - 556

Tissue	Macroscopic Observation
Gross Lesions Including Palpable Masses	Ventral left lower abdominal; Mass
	Dorsal right upper thorax; Mass
	Dorsal left upper thorax; No Mass Present
Remaining tissues	No abnormalities detected

Tissue	Microscopic Observation
Adrenal	Focal hypertrophy cortical cells
Cervical lymph node	Myelopoiesis
Gall bladder	Focal epithelial hyperplasia (minimal)
Harderian gland	Atrophy (foci/areas)
Heart	Myocarditis/fibrosis (minimal)
	Vacuolation myocardial fibres (minimal)
Kidney	Groups of basophilic tubules (minimal)
	Mononuclear cell foci (minimal)
Lacrimal gland	Mononuclear cell foci (minimal)
Liver	Mononuclear cell foci (minimal)
Lung	Perivascular/peribronchiolar lymphocytes (slight)
	Accumulations alveolar macrophages (moderate)
	MALIGNANT TUMOUR Adenocarcinoma
Mass 1	See preputial gland
Mass 2	No evidence gross lesion
Mass 3	No evidence gross lesion
Mesenteric lymph node	Myelopoiesis
Nasal cavities	Exudate overlying epithelium
Preputial gland	Abscess formation
Seminal vesicle	Reduced secretory content vesicle 1
	Reduced secretory content vesicle 2
Spleen	Extramedullary haemopoiesis (slight)
Testis	Atrophy Testis 1 (minimal)
Thyroid	Distension/coalescence follicles
Trachea	Dilatation subepithelial glands
	Number of Sections less than protocol for Adrenal (1), Mammary gland (0), Pituitary (0).

GLYPHOSATE TECHNICAL : DIETARY CARCINOGENICITY STUDY IN THE MOUSE

Appendix 9 (continued) Individual Clinical and Pathological Findings

Animal Number: 171

Dose Level: 5000 ppm **Sex:** Male

Day of Death: 558 **Fate:** Terminal kill

Clinical Findings	Day of Observations (Onset - Completion)
Mass	451 - 514
Scab	171 - 176
Generalised fur loss	171 - 178

Tissue	Macroscopic Observation
Gross Lesion Including Palpable Masses	M1 regressed mass VR10 retained
	Ventral left inguinal/pelvic region; No mass present
Lungs (With Bronchi)	Reddened
Remaining tissues	No abnormalities detected

Tissue	Microscopic Observation
Bone marrow	Adipose infiltration (minimal)
Brain	Focal mineralisation
Epididymis	Reduced spermatozoal content epididymis 1
	Reduced spermatozoal content epididymis 2
Harderian gland	Mononuclear cell foci (minimal)
	Atrophy (foci/areas)
Heart	Myocarditis/fibrosis (minimal)
	Vacuolation myocardial fibres (minimal)
Kidney	Groups of basophilic tubules (slight)
	Mononuclear cell foci (minimal)
Liver	Mononuclear cell foci (minimal)
Lung	Perivascular/peribronchiolar lymphocytes (minimal)
Mass 1	No evidence gross lesion
Nasal cavities	Exudate overlying epithelium
Prostate	Focal epithelial hyperplasia/atrophic change (minimal)
Seminal vesicle	Mononuclear cell foci (slight)
Spleen	Extramedullary haemopoiesis (slight)
Testis	Atrophy testis 1 (marked)
	Atrophy testis 2 (marked)
	Interstitial cell hyperplasia (minimal)
Trachea	Dilatation subepithelial glands
	Number of Sections less than protocol for Mammary gland (0), Thymus (0).