kidneys, liver and lungs of animals at the lowest (200 mg/kg) and intermediate (1000 mg/kg) doses underwent a full histopathological examination.

No treatment-related mortalities, clinical signs, haematological or biochemical findings and no organ-weight changes were observed. Gross or histopathological examination did not show any effects of glyphosate administration.

Taking into account the limited range of clinical chemistry parameters evaluated, the NOAEL in the 13-week toxicity study in mice was 4500 mg/kg bw per day, the highest dose tested in this study (Perry et al., 1991a).

In a 13-week oral toxicity study, groups of 10 male and 10 female B6C3F1 mice were fed diets containing glyphosate (purity 99%) at concentrations of 0, 3125, 6250, 12 500, 25 000 or 50 000 ppm (equal to 0, 507, 1065, 2273, 4776 and 10 780 mg/kg bw per day for males and 0, 753, 1411, 2707, 5846 and 11 977 mg/kg bw per day for females). All tissues from the highest-dose and control animals were examined microscopically. The salivary glands were also examined in all groups receiving lower doses.

Reduced body-weight gain was observed at 25 000 and 50 000 ppm in both males and females. There were no differences in feed consumption between control and treated mice. The only significant gross finding in the study was a "dark" salivary gland in a male at the highest dose; no other gross abnormalities were observed at necropsy. Histological changes were observed only in the parotid salivary gland (Table 11). The cytoplasmic alterations consisted of a diffuse increase in the basophilia of the acinar cells. In more severely affected glands, the cells and acini also appeared to be enlarged and had fewer ducts. No histological changes were observed in the submandibular and sublingual glands.

Table 11. Incidence and severity of cytoplasmic alteration of the parotid and submandibular salivary glands (combined) in mice administered glyphosate for 13 weeks

	No. of cases per dietary concentration of glyphosate					
	0 ppm	**3 125 ppm**	**6 250 ppm**	**12 500 ppm**	**25 000 ppm**	**50 000 ppm**
Males	0/10	010	5/10 (1.0)	9/10 (1.6)	10/10 (2.8)	10/10 (4.0)
Females	0/10	0/10	2/10 (1.0)	9/10 (1.3)	10/10 (2.4)	10/10 (3.1)

no.: number; ppm: parts per million

Results presented as number of mice showing cytoplasmic alterations / total number of mice in the group, with average severity score in parentheses. Severity score is based on a scale of 1 = minimal, 2 = mild, 3 = moderate or 4 = marked.

Source: Chan & Mahler (1992)

The NOAEL in the 13-week toxicity study in mice was 3125 ppm (equal to 507 mg/kg bw per day) based on parotid salivary gland lesions at 6250 ppm (equal to 1065 mg/kg bw per day) (Chan & Mahler, 1992).

In a 13-week oral toxicity study, groups of 12 male and 12 female ICR(Crj:CD-1)SPF mice were administered glyphosate (purity 97.56%) at dietary concentrations of 0, 5000, 10 000 or 50 000 ppm (equal to a mean daily glyphosate intake of 0, 600, 1221 and 6295 mg/kg bw per day for males and 0, 765, 1486 and 7435 mg/kg bw per day for females).

There were no treatment-related clinical signs, mortality or ophthalmological and haematological findings. At 50 000 ppm, mean body weights of the males were 91% that of the controls from week 2 to the end of the treatment; body weights of females were comparable to that of the controls. Similarly, feed consumption was slightly decreased in males at the highest dose. At

There were no statistically significant increases in the incidence of any tumours, benign and malignant, in either sex; however, the number of animals with multiple tumour types was slightly increased in the high-dose group of both sexes (males: 16/50; females: 11/50) compared to the control (males: 11/50; females: 6/50). This led to a slight increase in the total number of tumours in the high-dose group of both sexes (males: 60; females: 43) compared to the control (males: 49; females: 36).

Haemangiosarcoma in the vascular system was evident in 4/50 high-dose males, 2/50 low-dose females and 1/50 high-dose females compared to 0/50 controls. Of the high-dose mice, one had tumours in the liver and spleen; one had a tumour in the liver only; one had tumours in the liver, spleen and prostate; and one had a tumour in the spleen only. The incidence of haemangiosarcoma in males was positive in Exact trend test and nonsignificant in pairwise comparison (Table 21). In female mice, incidence of haemangiosarcoma did not achieve statistical significance.

Table 21. Haemangiosarcomas in male mice administered glyphosate for 104 weeks

	Measure per dietary dose of glyphosate			
	0 mg/kg bw per day	**100 mg/kg bw per day**	**300 mg/kg bw per day**	**1 000 mg/kg bw per day**
Haemangiosarcomas	0/47 (0%)	0/46 (0%)	0/50 (0%)	4/45 (9%)
	$P = 0.002\ 96$**	$P = 1.000\ 00$	$P = 1.000\ 00$	$P = 0.053\ 32$

bw: body weight; **: significance of trend ($P < 0.01$) denoted at control, using Fisher Exact test and Exact Trend test.

Results presented as number of tumour-bearing animals / number of animals examined less those that died before week 52, with the resulting percentage in parentheses.

Source: Atkinson et al., 1993a

Histiocytic sarcoma in the lymphoreticular/haematopoietic tissue was evident in 2/50 low- and high-dose males and 3/50 low- and intermediate-dose females and 1/50 high-dose female (none were evident in the respective controls). Due to a lack of dose relationship and statistical significance, these changes are not considered treatment related. Other tumours seen were considered typical for mice of this age and strain.

The NOAEL for systemic toxicity in the 104-week carcinogenicity study in mice was 1000 mg/kg bw per day, the highest dose tested (Atkinson et al., 1993a).

In an 18-month carcinogenicity study, glyphosate (two lots of HR-001, purity 97.56% and 94.61%) was fed in the diet to groups of 50 male and 50 female ICR(Crj:CD-1)(SPF) mice at 0, 1600, 8000 or 40 000 ppm (equal to 0, 165, 838.1 or 4348 mg/kg bw per day for males and 0, 153.2, 786.8 or 4116 mg/kg bw per day for females) for 18 months. During treatment, all animals were observed for clinical signs and changes in body weight, and feed consumption was measured. At week 21, urine analysis was carried out on 20 males from all groups. Differential leukocyte counts were determined in blood smears from 10 males and 10 females from all groups at week 52 and after 78 weeks of treatment and also in animals terminated in extremis during the treatment, as possible. At final necropsy after 78 weeks of treatment, organ weights of 10 males and 10 females were analysed to determine differential leukocyte counts. All animals of both sexes were necropsied and their histopathology examined.

At 1600 ppm, there were no treatment-related changes in either sex in any parameters. At 8000 ppm, retarded growth was observed in females with statistically significant decreases in weight at week 6 and weeks 9 to 24. No treatment-related changes were seen in males. At 40 000 ppm, the incidence of pale skin increased in males. In addition, loose stools were found in all the cages from week 21 in males and week 20 in females. Retarded growth was persistently observed during treatment, with statistically significant differences in weight from week 16 to 36 in males and from week 6 to the end of the treatment in females. These changes were associated with depressed feed