consumption was reduced for males at the intermediate and highest dose during the first week of the study. Feed intake for treated females was comparable to that of controls throughout the study. The only clinical signs of toxicity were soft stools and/or diarrhoea, which occurred in both sexes at all doses with diarrhoea being the predominant sign in animals at the highest dose during the last 3 weeks of the study. Gross and microscopic pathology examinations revealed no treatment-related lesions.

Because of the frequent occurrence of soft stools and/or diarrhoea at all doses, no NOAEL could be derived from this 4-week dietary toxicity study in rats (Reyna & Thake, 1989).

In a 4-week oral toxicity study, groups of five male and five female Sprague Dawley rats were fed diets containing glyphosate (purity 99.5%) at a concentration that was adjusted weekly to give doses of 0, 50, 250, 1000 or 2500 mg/kg bw per day. All the animals were terminated and necropsied, and the livers, hearts, kidneys, spleens and adrenals of control and highest-dose animals processed and examined histopathologically. Examination was subsequently extended to include the kidneys from all females in all the groups.

Soft faeces were noted in three males in the highest-dose group during weeks 3 to 4, but not in any other group. No treatment-related effects were observed on mortality, clinical signs of toxicity, body weights, feed and water consumption or haematological parameters. In males, equivocal increases in plasma alanine transaminase [alanine aminotransferase] and alkaline phosphatase activities were observed at 250, 1000 or 2500 mg/kg bw. In females, plasma alanine transaminase activity was significantly increased at the highest dose, as was total bilirubin. In addition, increased plasma concentrations of phosphate were noted in males at 1000 or 2500 mg/kg bw. There were neither notable intergroup differences in organ weights nor gross pathological findings. However, an increase in the incidence of very mild to slight nephrocalcinosis was observed in female rats at 250 mg/kg bw and higher doses (Table 13).

Table 13. Nephrocalcinosis in rats administered glyphosate for 4 weeks

	No. per dietary concentration of glyphosate									
	Males					**Females**				
	0 mg/kg bw per day	**50 mg/kg bw per day**	**250 mg/kg bw per day**	**1 000 mg/kg bw per day**	**2 500 mg/kg bw per day**	**0 mg/kg bw per day**	**50 mg/kg bw per day**	**250 mg/kg bw per day**	**1 000 mg/kg bw per day**	**2 500 mg/kg bw per day**
No. of cases	0	NI	NI	NI	NI	0	0	2	2	4
No. of very mild/minimal cases	0	NI	NI	NI	NI	0	0	1	1	2
No. of mild/slight cases	0	NI	NI	NI	NI	0	0	1	1	2

bw: body weight; NI: not investigated; no.: number

Source: Atkinson et al. (1989)

The NOAEL in the 4-week dietary toxicity study in rats was 50 mg/kg bw per day for slight nephrocalcinosis in female rats at 250 mg/kg bw per day (Atkinson et al., 1989). This finding was not confirmed in a separate study by Perry et al., 1991b.

In a 90-day oral toxicity study, groups of 12 male and 12 female Sprague Dawley rats were fed diets containing glyphosate (purity 95.2%) at concentrations of 0, 1000, 5000 or 20 000 ppm (calculated mean intakes equal to 0, 63, 317 and 1267 mg/kg bw per day for males and 0, 84, 404 and 1623 mg/kg bw per day for females). Clinical signs, body weight, feed consumption, haematology

An increased incidence of thyroid C-cell adenomas was observed at 8000 and 20 000 ppm in both sexes but this did not reach statistical significance compared to the control animals (Table 29). There was a statistically significant dose trend for C-cell adenomas and adenomas/carcinomas combined in females. The testing laboratory historical control range for C-cell adenomas was 1.8–10.6% for males and 3.3–10% for females; the range for C-cell carcinomas was 0–5.2% for males and 0–2.9% for females. These tumours are not considered relevant to human risk assessment because 1) the increased incidences in males were not statistically significant; 2) there was no evidence of progression from adenoma to carcinoma; 3) and there were no dose-related increases in the incidence or severity of pre-neoplastic lesions (hyperplasia); and 4) they occurred in only one study.

Table 29. Thyroid C-cell tumours in male and female rats administered glyphosate for 24 months

		Incidence per dietary concentration of glyphosate			
Finding	**Sex**	**0 ppm**	**2 000 ppm**	**8 000 ppm**	**20 000 ppm**
Adenoma	M	2/54 (4%)	4/55 (7%)	8/58 (14%)	7/58 (12%)
	F	2/57 (4%)*	2/60 (3%)	6/59 (10%)	6/55 (11%)
Carcinoma	M	0/54 (0%)	2/55 (4%)	0/58 (0%)	1/58 (2%)
	F	0/57 (0%)	0/60 (0%)	1/59 (2%)	0/55 (0%)
Adenoma + carcinoma (combined)	M	2/54 (4%)	6/55 (11%)	8/58 (14%)	8/58 (14%)
	F	2/57 (4%)*	2/60 (3%)	7/59 (12%)	6/55 (11%)

F: females; M: males; ppm: parts per million; *: $P < 0.05$ (Cochran–Armitage Trend Test)

Results presented as number of rats affected / number of animals examined, excluding those that died or were terminated prior to study week 55, and the resulting percentage in parentheses.

Source: Strout & Ruecker (1990)

The incidence of benign keratoacanthoma was increased in male rats, but as there was no dose–response relationship, it was not considered treatment related (Table 30).

Table 30. Skin keratoacanthoma in male rats administered glyphosate for 24 months

	Incidence per dietary concentration of glyphosate			
Finding	**0 ppm**	**2 000 ppm**	**8 000 ppm**	**20 000 ppm**
Benign keratoacanthoma (dead and moribund animals)	0/36 (0%)	1/31 (3%)	2/33 (6%)	1/32 (3%)
Benign keratoacanthoma (terminal kill)	0/13 (0%)	2/19 (11%)	2/17 (12%)	2/17 (12%)

ppm: parts per million

Results presented as number of rats with skin keratoacanthoma / number of rats assessed, with the resulting percentage in parentheses.

Source: Strout & Ruecker (1990)

Lymphoma/lymphosarcoma was observed in multiple tissues in male and female rats; however, the incidences in treatment groups were lower than in the controls and no dose relationship was observed.

The NOAEL for toxicity in rats was 8000 ppm (equal to 362 mg/kg bw per day) for decreased body-weight gains in females and cataractous lens changes in males seen at the LOAEL of 20 000 ppm (Strout & Ruecker, 1990).

glyphosate was not used (Paz-y-Mino et al., 2007). The samples were collected from exposed individuals 2 weeks to 2 months after the spraying had occurred. In reviewing the study, the JMPR committee noted that the study had some major deficiencies; the blood samples of the two groups were collected and processed at different times, a key consideration for an assay that is highly prone to technical artefacts during sample preparation. In addition, the two populations were located at considerable distance from each other, the background frequencies of DNA breakage in these communities was not known, and the median DNA migration values were identical for 20 of the 21 subjects in the control population, a result that was considered to be highly unusual.

The JMPR committee concluded that the study was inconclusive as problems with study design severely limit the conclusions that can be drawn.

In a follow-up study by the same authors, the frequency of structural chromosomal aberrations in peripheral blood lymphocytes was measured in the study population that two years previously had been exposed to glyphosate; the frequencies were found to be normal (Paz-y-Mino, 2011). The study results were considered to be negative but minimally informative as many types of chromosome alterations do not persist for extended periods of time.

In another study, the levels of 8-OHdG, a lesion formed from oxidative damage to DNA, were measured in the peripheral blood lymphocytes of workers spraying glyphosate (Koureas et al., 2014). A modestly elevated but statistically nonsignificant increase was reported.

Summaries of these biomonitoring studies are shown in Table 36.

Table 36. Summary of human biomonitoring studies

End-point	Test object	Concentration	Purity	GLP (Yes/ No)	Results	Reference
Structural chromosomal aberrations	Human peripheral blood cells	Aerial spraying, Ecuadorian region bordering Colombia	Glyphosate-containing mixture	No	Negative	Paz-y-Mino et al. (2011)
Micronucleus	Human peripheral blood lymphocytes	Aerial spraying, Narino, Colombia	Herbicide mixtures containing glyphosate and adjuvant	No	Equivocal/inconclusive	Bolognesi et al. (2009)
Micronucleus	Human peripheral blood lymphocytes	Aerial spraying, Putumayo, Colombia	Herbicide mixtures containing glyphosate and adjuvant	No	Equivocal / inconclusive	Bolognesi et al. (2009)
Micronucleus	Human peripheral blood lymphocytes	Aerial spraying, Valle del Cuaca, Colombia	Roundup 47	No	Equivocal / inconclusive	Bolognesi et al. (2009)
DNA strand breaks/Comet	Human peripheral blood cells	Aerial spraying, Ecuadorian region bordering Colombia	Roundup Ultra (44%)	No	Equivocal/ inconclusive	Paz-y-Mino et al. (2007)
DNA adducts (8-OHdG)	Human peripheral blood cells	Pesticide applicators	Glyphosate	No	Negative	Koureas et al. (2014)

8-OHdG: 8-hydroxy-2'-deoxyguanosine