3.2 GLYPHOSATE (158)

TOXICOLOGY

Glyphosate is the ISO-approved common name for *N*-(phosphonomethyl)glycine (IUPAC), with CAS number 1071-83-6. It is a broad-spectrum systemic herbicide.

Glyphosate was previously evaluated by JMPR for toxicology in 1986, 1997 (evaluation of the metabolite aminomethylphosphonic acid, or AMPA), 2004 and 2011 (evaluation of new plant metabolites in genetically modified maize and soya beans).

Glyphosate was last re-evaluated for toxicology within the periodic review programme of CCPR in 2004. The compound was reviewed by the present Meeting following the recommendation of an electronic task force of the WHO Core Assessment Group on Pesticide Residues that it be re-evaluated due to public health concerns identified by IARC and the availability of a significant number of new studies.

The current Meeting evaluated all previously considered toxicological data in addition to new published or unpublished toxicological studies and published epidemiological studies on cancer outcomes. The evaluation of the biochemical aspects and systemic toxicity of glyphosate was based on previous JMPR evaluations, updated as necessary with additional information. The particular focus of the current meeting was on genotoxicity, carcinogenicity, reproductive and developmental toxicity and epidemiological studies on cancer outcomes. The scope was restricted to the active ingredient.

All critical unpublished studies contained statements of compliance with GLP, unless otherwise specified. The studies on human volunteers were conducted in accordance with the principles expressed in the Declaration of Helsinki or equivalent ethical standards.

Biochemical aspects

In studies with radiolabelled glyphosate in rats, glyphosate was rapidly absorbed from the gastrointestinal tract following oral intake, but only to a limited extent (about 20–30%). Elimination was fast and virtually complete within 72–168 hours, with the majority being excreted during the first 48 hours. Most of the excretion occurred in faeces, largely as unabsorbed dose, and in the urine. Biliary excretion of glyphosate was negligible. Less than 1% of the administered dose was retained in tissues 168 hours post-administration. Highest residues were detected in bone, followed by kidney and liver. This pattern of absorption, distribution and elimination was independent of dose, treatment regimen and sex of the test animals. Peak plasma concentrations of radiolabel were observed at 6 and 2 hours after administration in male and female rats, respectively. The estimated half-life for whole-body elimination of the radiolabel was about 5.9–8.3 hours.

There was very little biotransformation of glyphosate; the only metabolite, AMPA, accounted for 0.2–0.7% of the administered dose in excreta; the rest was unchanged glyphosate.

Toxicological data

Glyphosate has low acute oral toxicity in mice (LD_{50} > 2000 to > 10 000 mg/kg bw; no lethality at 2000 mg/kg bw) and rats (LD_{50} 5600 mg/kg bw), low acute dermal toxicity in rats (LD_{50} > 2000 mg/kg bw) and rabbits (LD_{50} > 5000 mg/kg bw), and low acute inhalation toxicity in rats (LC_{50} > 5.48 mg/L). Glyphosate was not irritating to the skin of rabbits. Glyphosate produced moderate to severe eye irritation in rabbits, with irreversible corneal opacity in one study as a consequence of the low pH of the test material in solution. Glyphosate was not sensitizing in guinea-pigs or mice as determined by the Magnusson and Kligman maximization test, the Buehler test and the local lymph node assay.

In short-term studies of toxicity in different species, the most notable effects were clinical signs related to gastrointestinal irritation, decreased body weight, salivary gland changes (hypertrophy and increase in basophilia of cytoplasm of acinar cells), histological findings in the caecum and hepatotoxicity.

In short-term studies in mice, reduced body weight was seen at a dietary concentration of 50 000 ppm (equal to 9710 mg/kg bw per day). The NOAEL for decreased body weight was 10 000 ppm (equal to 1221 mg/kg bw per day). Effects on the salivary glands were observed in mice in only one study out of four at 6250 ppm (equal to 1065 mg/kg bw per day). The NOAEL for the salivary gland effects in mice was 3125 ppm (equal to 507 mg/kg bw per day). The overall NOAEL in short-term studies in mice was 3125 ppm (equal to 507 mg/kg bw per day), and the overall LOAEL was 6250 ppm (equal to 1065 mg/kg bw per day).

In 90-day toxicity studies in rats, common findings included soft faeces, diarrhoea, reduced body weight gain and decreased food utilization at dietary concentrations of 20 000 ppm (equal to 1262.1 mg/kg bw per day) and above. The lowest NOAEL was 371.9 mg/kg bw per day. A decrease in urine pH was frequently noted owing to the acidic nature of the compound and excretion as glyphosate in the urine. In two 90-day dietary toxicity studies, an increase in caecum weight (at 10 000 ppm, equal to 569 mg/kg bw per day) and histological findings in the caecum (at 50 000 ppm, equal to 3706 mg/kg bw per day) were observed. In rats, effects on the salivary gland were seen in two out of seven 90-day studies starting at 12 500 ppm (equal to 811 mg/kg bw per day). The NOAELs for effects on the salivary gland were 300 and 410 mg/kg bw per day. The overall NOAEL in short-term studies in rats was 300 mg/kg bw per day, and the overall LOAEL was 10 000 ppm (equal to 569 mg/kg bw per day).

In four 90-day toxicity studies in dogs, the most notable effects were loose stools, decreased body weight and reduced feed consumption. In one study, there were no treatment-related effects at doses up to 40 000 ppm (equal to 1015 mg/kg bw per day). The lowest NOAEL and LOAEL were 300 mg/kg bw per day and 1000 mg/kg bw per day, respectively.

Seven 1-year toxicity studies in dogs are available. In one study, changes in faeces were observed at 100 mg/kg bw per day and above. The NOAEL was 30 mg/kg bw per day. However, these results were not reproduced in four other studies with administration via capsules at 300 or 500 mg/kg bw per day. In the remaining six studies, the NOAELs ranged from 8000 ppm (equal to 182 mg/kg bw per day) to 500 mg/kg bw per day, and the LOAELs ranged from 30 000 ppm (equal to 926 mg/kg bw per day) to 1000 mg/kg bw per day.

The overall NOAEL in the 90-day and 1-year toxicity studies in dogs was 15 000 ppm (equal to 448 mg/kg bw per day), and the overall LOAEL was 30 000 ppm (equal to 926 mg/kg bw per day).

The Meeting compiled the tumour incidence data for all relevant mouse and rat studies in order to undertake statistical analysis and investigate any potential pattern of occurrence across studies. In addition, incidences of tumours of lymphatic tissues were summarized, as these were identified as possible targets of relevance from the review of epidemiological cancer studies. However, the Meeting recognized that the relationship between tumours of lymphatic tissues in rodents and humans has not been clearly established.

Nine carcinogenicity studies in mice were available. Two studies were considered to be of insufficient quality to be included in the assessment. Effects such as loose stools, reduced body weights and decreased feed consumption were noted in most of the studies. The overall NOAEL for systemic toxicity in mice was 1600 ppm (equal to 153 mg/kg bw per day), and the overall LOAEL was 8000 ppm (equal to 787 mg/kg bw per day).

The Meeting concluded that there is equivocal evidence of induction of lymphomas in male mice in three out of seven studies and in female mice in one out of seven studies at high doses (5000–40 000 ppm, equal to 814–4348 mg/kg bw per day). The Meeting also noted that in the other three studies in which even higher doses (up to 50 000 ppm, equal to 7470 mg/kg bw per day) had been used, no effect was observed.

The Meeting concluded that there is some indication, by a trend test, and not by pairwise comparison, of induction of kidney adenomas in male mice in four out of seven studies. The Meeting noted that the increases were marginal and occurred at the highest dose only and that other studies that used appreciably higher doses did not find any excess. However, the Meeting noted that kidney adenomas are uncommon in male mice.

Eleven combined chronic toxicity and carcinogenicity studies in rats were available. One study was considered to be inadequate for carcinogenicity assessment due to its exposure duration (12 months). Toxicities variously reported in some of these studies included increased incidences of clinical signs, reduced body weights, degenerative lens changes (cataracts) in males, microscopic findings in the salivary gland, increased incidence of basophilia of parotid acinar cells, and microscopic findings in liver, prostate and kidneys. The overall NOAEL for systemic toxicity in rats was 100 mg/kg bw per day, and the overall LOAEL was 300 mg/kg bw per day.

The Meeting discussed the increased incidence of a variety of tumours observed in one or, in one case, two of the 10 studies in rats. The Meeting concluded that these findings were incidental, based on the following considerations:

- interstitial cell tumours of the testes: occurred in only one study; and other studies that used appreciably higher doses did not find any excess;
- pancreatic islet cell adenoma: occurred in only one study in males only; other studies that used appreciably higher doses did not find any excess; there was no dose–response relationship; and the incidence in controls was unusually low (less than the lower bound of the historical control data); the Meeting also noted that there was a negative dose–response relationship in females;
- thyroid C-cell tumours: occurred in only one study; other studies that used appreciably higher doses did not find any excess; and these tumours are considered not to be relevant for humans;
- skin keratoma: occurred in two studies in males only; other studies that used appreciably higher doses did not find any excess; in one study, there was no dose–response relationship; and in the other study, only the test for trend was statistically significant, not the pairwise test at any dose;
- lymphoma (in spleen and kidney): no evidence of induction in any of the studies.

The Meeting concluded that there is no reliable evidence for treatment-related tumours in rats at doses up to 32 000 ppm (equal to 1750 mg/kg bw per day).

The Meeting concluded that glyphosate is not carcinogenic in rats but could not exclude the possibility that it is carcinogenic in mice at very high doses.

Glyphosate and its formulation products have been extensively tested for genotoxic effects using a variety of tests in a wide range of organisms. While no mutational effects have been detected in bacterial test systems, DNA damage and chromosomal effects have commonly been seen in cell culture models and in organisms that are phylogenetically distant from humans. However, these effects have not been seen in vivo in orally treated mammalian models. The overall weight of evidence indicates that administration of glyphosate and its formulation products at doses as high as 2000 mg/kg bw by the oral route, the route most relevant to human dietary exposure, was not associated with genotoxic effects in an overwhelming majority of studies conducted in mammals, a model considered to be appropriate for assessing genotoxic risks to humans.

The Meeting concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures.

Seven reproductive toxicity studies in rats were available. No evidence of reproductive toxicity was observed at doses up to 30 000 ppm (equal to 1983 mg/kg bw per day). In one study, an

increased incidence of histopathological findings in the parotid (males) and submaxillary salivary glands in females was observed in both generations at 10 000 ppm (equal to 668 mg/kg bw per day). The NOAEL was 3000 ppm (equal to 197 mg/kg bw per day). In a separate study, an increased incidence of loose stools and caecum distension was observed in both generations at 30 000 ppm (equal to 2150 mg/kg bw per day), and the NOAEL was 6000 ppm (equal to 417 mg/kg bw per day). Slight reductions in pup weight or weight gain were observed in most studies, but were confined to very high, parentally toxic dose levels. In addition, a significant delay in sexual maturation in male pups (F_1) was seen at 15 000 ppm (equal to 1063 mg/kg bw per day). The overall NOAEL for parental toxicity was 6000 ppm (equal to 417 mg/kg bw per day), and the overall LOAEL was 10 000 ppm (equal to 668 mg/kg bw per day). The overall NOAEL for offspring toxicity was 6000 ppm (equal to 417 mg/kg bw per day), and the overall LOAEL was 10 000 ppm (equal to 985 mg/kg bw per day).

No evidence of teratogenicity was observed in four developmental toxicity studies in rats at doses up to 3500 mg/kg bw per day. There was some variation in the extent of toxicity observed in the four studies. The lowest NOAEL for maternal toxicity was 300 mg/kg bw per day, based on loose stools and reduced body weights seen at 1000 mg/kg bw per day. The lowest NOAEL for embryo and fetal toxicity was 300 mg/kg bw per day, based on delayed ossification and an increased incidence of fetuses with skeletal anomalies observed at 1000 mg/kg bw per day.

Seven developmental toxicity studies in the rabbit were available. Maternal toxicity was primarily manifested as an increased incidence of soft stools and diarrhoea at doses of 175 mg/kg bw per day and above. The overall NOAEL for maternal toxicity was 100 mg/kg bw per day. In three studies, the occurrences of a variety of low-incidence fetal effects (e.g. cardiac malformation, absent kidney) were slightly increased at higher dose levels. These increases are considered secondary to maternal toxicity. The overall NOAEL for embryo and fetal toxicity was 250 mg/kg bw per day, based on effects at 450 mg/kg bw per day. The Meeting considered that these effects were secondary to local irritation from unabsorbed glyphosate in the colon administered by gavage dosing and concluded that they were not relevant for establishing health-based guidance values.

The Meeting concluded that glyphosate is not teratogenic.

Glyphosate was tested in a range of validated in vivo and in vitro assays for its potential to interact with the endocrine system. The studies that the Meeting considered adequate for the evaluation clearly demonstrate that there is no interaction with estrogen or androgen receptor pathways or thyroid pathways.

There was no evidence of neurotoxicity in an acute neurotoxicity study in rats at doses up to 2000 mg/kg bw. The NOAEL for systemic toxicity was 1000 mg/kg bw, based on a single death and general signs of toxicity at 2000 mg/kg bw. In a 90-day neurotoxicity study in rats, no evidence of neurotoxicity or systemic toxicity was seen at doses up to 20 000 ppm (equal to 1546.5 mg/kg bw per day).

No evidence of immunotoxicity was seen in a 28-day dietary study in female mice at doses up to 5000 ppm (equal to 1448 mg/kg bw per day).

Effects on the salivary glands were observed in several repeated-dose toxicity studies in rats. The pH of glyphosate in solution is low, and it has been shown that exposure to organic acids can cause such changes in salivary glands. Therefore, the changes are likely secondary to the effects caused by the pH of the test compound in solution.

In many of the long-term repeated-dose studies reviewed, glyphosate was reported to have an impact on the gastrointestinal tract at high doses. Although this is not uncommon with high-dose chemical substance administration, this was investigated further, as glyphosate is known to be poorly absorbed in mammalian models, and alterations in gut microbiota profiles, specifically reductions in the beneficial microbiota and increases in pathogenic bacteria, are known to have impacts on carcinogenesis. There is evidence from livestock species that pathogenic bacteria are more resistant to glyphosate, whereas beneficial microbiota are more sensitive, and thus more vulnerable.

This is an emerging area of scientific investigation. The extent to which glyphosate adversely affects the normal functioning of the microbiota in the human gastrointestinal tract or the gastrointestinal tract of mammalian models is unclear. However, it is unlikely, given the available information on minimum inhibitory concentration (MIC) values, that this would occur from glyphosate residues in the diet.

Toxicological data on metabolites and/or degradates

AMPA is the only identified metabolite found in the urine and faeces of orally treated rats. AMPA was of low acute oral and dermal toxicity in rats (LD_{50} > 5000 and > 2000 mg/kg bw, respectively) and was not sensitizing in guinea-pigs, as determined by the Magnusson and Kligman maximization test. In a 90-day study of toxicity in rats, the NOAEL was 1000 mg/kg bw per day, the highest dose tested. AMPA administered orally in mammalian test systems showed no evidence of genotoxicity. Largely negative results were seen in studies in vitro. The Meeting concluded that AMPA is unlikely to be genotoxic in vivo by the oral route. In a study of developmental toxicity in rats, no evidence for embryo or fetal toxicity was observed; the NOAEL for maternal and embryo/fetal toxicity was 1000 mg/kg bw per day, the highest dose tested.

Following single gavage administration of radiolabelled *N*-acetyl-glyphosate, a plant-specific metabolite, at 15 mg/kg bw in rats, about 66.1% of the administered dose was excreted in urine (61.3% within 12 hours post-dosing), 26.4% in faeces (25.8% within 48 hours post-dosing), 2.79% in cage wash and wipe, and 0.23% in residual carcass. Radioactivity was eliminated rapidly from blood and plasma, with half-life values of 20.1 and 15.6 hours, respectively. Unchanged [^{14}C]*N*-acetyl-glyphosate recovered in urine and faeces represented over 99% of the administered radioactivity. Glyphosate, a metabolite of *N*-acetyl-glyphosate, was detected in faeces and represented less than 1% of the total radioactivity.

The acute oral toxicity LD_{50} of *N*-acetyl-glyphosate in rats is greater than 5000 mg/kg bw, expressed as the free acid. In a 90-day toxicity study in rats, the NOAEL was 18 000 ppm (equal to 1157 mg/kg bw per day).

N-Acetyl-glyphosate was tested for genotoxicity in vitro and in vivo in an adequate range of assays; it was not found to be genotoxic in mammalian or microbial test systems.

The Meeting concluded that *N*-acetyl-glyphosate is unlikely to be genotoxic.

N-Acetyl-AMPA, another plant-specific metabolite, was of low acute oral toxicity; the LD_{50} was greater than 5000 mg/kg bw in rats.

N-Acetyl-AMPA was tested for genotoxicity in vitro and in vivo in an adequate range of assays; it was not found to be genotoxic in mammalian or microbial test systems.

The Meeting concluded that *N*-acetyl-AMPA is unlikely to be genotoxic.

Human data

Routine medical surveillance of workers in production and formulation plants revealed no adverse health effects attributable to glyphosate. In operators applying glyphosate products, cases of eye, skin and/or respiratory tract irritation have been reported. Acute intoxication was reported in humans after accidental or intentional ingestion of concentrated glyphosate formulations, resulting in gastrointestinal, cardiovascular, pulmonary and renal effects and, occasionally, death. The acute toxicity of glyphosate formulations was likely caused by the surfactant in these products.

Several epidemiological studies on cancer outcomes following occupational exposure to glyphosate were available. The evaluation of these studies focused on the occurrence of NHL, as outlined in section 2.2. One meta-analysis and one prospective cohort study, the AHS, with a large sample size and detailed exposure assessment, were available. Cohort studies are considered a

powerful design, as recall bias is avoided. All other studies were case–control studies, usually retrospective, which are more prone to recall and selection biases.

The AHS cohort study found no evidence of a positive association of NHL with glyphosate exposure or an exposure–response relationship. Elevated risks were reported in various case–control studies. A significant elevated risk of NHL associated with ever versus never use of glyphosate (odds ratio [OR] = 2.1; 95% CI = 1.1–4.0) was reported. Ever use of glyphosate was not associated with risk of NHL in the cross-Canada case–control study of pesticides and health, but when analysing days of use per year, there was a significant elevated risk in the highest usage category (OR = 2.12; 95% CI = 1.20–3.73; for > 2 days/year glyphosate use). There was, however, no indication of an exposure–response relationship across exposure usage categories. In another case–control study, a significant increased risk of NHL associated with ever use (OR = 2.02; 95% CI = 1.10–3.71) as well as the highest usage category (OR = 2.36; 95% CI = 1.04–5.37; for greater than 10 days/year glyphosate use) was observed, with some suggestion of an exposure–response gradient. Two smaller case–control studies with few exposed cases and limited statistical power reported a non-significant elevated risk and no association, respectively, for risk of NHL and ever use of glyphosate. The meta-analysis, including the AHS, found a significant 50% excess risk ratio for ever versus never use of glyphosate.

Overall, there is some evidence of a positive association between glyphosate exposure and risk of NHL from the case–control studies and the overall meta-analysis. However, it is notable that the AHS, which is the only cohort study and is large and of high quality, found no evidence of association at any exposure level.

In view of the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans via exposure from the diet.

The Meeting concluded that the existing database on glyphosate was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

The Meeting reaffirmed the group ADI for the sum of glyphosate, AMPA, *N*-acetyl-glyphosate and *N*-acetyl-AMPA of 0–1 mg/kg bw on the basis of the NOAEL of 100 mg/kg bw per day for effects on the salivary gland in a long-term study of toxicity and carcinogenicity in rats and application of a safety factor of 100. The Meeting noted that these effects may be secondary to local irritation due to the low pH of glyphosate in solution, but was unable to establish this unequivocally.

The Meeting concluded that it was not necessary to establish an ARfD for glyphosate, AMPA, *N*-acetyl-glyphosate and *N*-acetyl-AMPA in view of their low acute toxicity, the absence of relevant developmental toxicity in rats and rabbits that could have occurred as a consequence of acute exposure, and the absence of any other toxicological effect that would be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment of glyphosate

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen- to 24-month studies of toxicity and carcinogenicity[a,b]	Toxicity	1 600 ppm, equal to 153 mg/kg bw per day[c]	8 000 ppm, equal to 787 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
		Carcinogenicity	The Meeting could not exclude the possibility that glyphosate is carcinogenic in mice at very high doses.	
Rat	Acute neurotoxicity study[a]	Neurotoxicity	2 000 mg/kg bw[c]	–
	Two-year studies of toxicity and carcinogenicity[b]	Toxicity	100 mg/kg bw per day	300 mg/kg bw per day
		Carcinogenicity	32 000 ppm, equal to 1 750 mg/kg bw per day[c]	–
	Two-generation studies of reproductive toxicity[a,b]	Reproductive toxicity	30 000 ppm, equal to 1 983 mg/kg bw per day[c]	–
		Parental toxicity	6 000 ppm, equal to 417 mg/kg bw per day	10 000 ppm, equal to 668 mg/kg bw per day
		Offspring toxicity	6 000 ppm, equal to 417 mg/kg bw per day	10 000 ppm, equal to 985 mg/kg bw per day
	Developmental toxicity studies[b,d]	Maternal toxicity	300 mg/kg bw per day	1 000 mg/kg bw per day
		Embryo and fetal toxicity	300 mg/kg bw per day	1 000 mg/kg bw per day
Rabbit	Developmental toxicity studies[b,d]	Maternal toxicity[e]	100 mg/kg bw per day	175 mg/kg bw per day
		Embryo and fetal toxicity[e]	250 mg/kg bw per day	450 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity[b,f]	Toxicity	15 000 ppm, equal to 448 mg/kg bw per day	30 000 ppm, equal to 926 mg/kg bw per day
AMPA				
Rat	Thirteen-week study of toxicity[d]	Toxicity	1 000 mg/kg bw per day[c]	–
	Developmental toxicity study[d]	Maternal toxicity	1 000 mg/kg bw per day[c]	–
		Embryo and fetal toxicity	1 000 mg/kg bw per day[c]	–

[a] Dietary administration.
[b] Two or more studies combined.
[c] Highest dose tested.
[d] Gavage administration.
[e] Secondary to local irritation of the colon.
[f] Capsule administration.

Estimate of acceptable daily intake (ADI)

0–1 mg/kg bw (for sum of glyphosate, *N*-acetyl-glyphosate, AMPA and *N*-acetyl-AMPA)

Estimate of acute reference dose (ARfD)

Unnecessary

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to glyphosate

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapidly, but only to a limited extent (about 20–30%)
Dermal absorption	About 1–3%
Distribution	Widely distributed (low levels occurring in all tissues)
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid and nearly complete in 48 h (about 20–30% in urine and about 60–70% in faeces)
Metabolism in animals	Very limited (< 0.7%), by hydrolysis leading to AMPA
Toxicologically significant compounds in animals and plants	Parent compound, AMPA, *N*-acetyl-glyphosate, *N*-acetyl-AMPA
Acute toxicity	
Rat, LD_{50}, oral	5 600 mg/kg bw
Rat, LD_{50}, dermal	> 2 000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.48 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Moderately to severely irritating
Guinea-pig, dermal sensitization	Not sensitizing (Magnusson and Kligman test, Buehler test)
Mouse, dermal sensitization	Not sensitizing (local lymph node assay)
Short-term studies of toxicity	
Target/critical effect	Clinical signs (loose stools, diarrhoea), liver, salivary glands and reduced body weights
Lowest relevant oral NOAEL	300 mg/kg bw per day (90 days; rat)
Lowest relevant dermal NOAEL	> 5 000 mg/kg bw per day (21 days; rabbit)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Reduced body weights, loose stools, liver (toxicity), salivary glands (organ weight, histology), eye (cataracts, lens fibre degeneration)
Lowest relevant NOAEL	100 mg/kg bw per day (2 years; rat)
Carcinogenicity	Not carcinogenic in rats; could not exclude possibility of carcinogenicity in mice at very high doses[a]

Genotoxicity	
	No genotoxic potential via oral route in mammals[a]
Reproductive toxicity	
Target/critical effect	Reduced body weights and delayed development (absence of maternal toxicity)
Lowest relevant parental NOAEL	417 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	417 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	1 983 mg/kg bw per day (rat)
Developmental toxicity	
Target/critical effect	Slight increase in malformations at maternally toxic doses
Lowest relevant maternal NOAEL	100 mg/kg bw per day (rabbit)[b]
Lowest relevant embryo/fetal NOAEL	250 mg/kg bw per day (rabbit)[b]
Neurotoxicity	
Acute neurotoxicity NOAEL	2 000 mg/kg bw, highest dose tested
Subchronic neurotoxicity NOAEL	1 547 mg/kg bw per day, highest dose tested
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity	No immunotoxicity; NOAEL 1 448 mg/kg bw per day, highest dose tested (28 days; mouse)
Studies on toxicologically relevant metabolites	Toxicological studies on AMPA, *N*-acetyl-glyphosate and *N*-acetyl-AMPA reveal the metabolites to be less toxic than the parent compound
Human data	
	Medical surveillance of workers in plants producing and formulating glyphosate did not reveal any adverse health effects. In operators applying glyphosate products, cases of eye, skin and/or respiratory irritation have been reported. Cases of acute intoxication have been observed after accidental or intentional ingestion of glyphosate formulation.

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.
[b] Secondary to local irritation of the colon.

Summary

	Value	Study	Safety factor
ADI	0–1 mg/kg bw	Two-year studies of toxicity (rat)	100
ARfD	Unnecessary	–	–

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The ADI for glyphosate is 0–1 mg/kg bw. The IEDIs for glyphosate were estimated for the 17 GEMS/Food cluster diets using the STMR or STMR-P values estimated by JMPR. The results are

shown in Annex 3. The IEDI ranged from 0% to 1% of the maximum ADI. The Meeting concluded that the long-term dietary exposure to residues of glyphosate from uses that have been considered by JMPR is unlikely to present a public health concern.

Short-term dietary exposure

The Meeting concluded that it was unnecessary to establish an ARfD for glyphosate, and therefore an IESTI for glyphosate was not calculated. The Meeting therefore concluded that short-term dietary exposure to glyphosate residues is unlikely to present a risk to consumers.