FOOD SAFETY

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Glyphosate

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of glyphosate (CAS No. 1071-83-6), an amino acid herbicide, based on results from various studies. Major adverse effects of glyphosate were observed on reduced gain of body weight, GI tract (diarrhea, increased cecum weight, bowel dilatation, thickening of intestinal mucosa), and liver (increased alkaline phosphatase (ALP), hepatocellular hypertrophy). Glyphosate had no neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity, and genotoxicity. As the whole, the lowest value among no-observed-adverse-effect levels (NOAELs) was 100 mg/kg bw/day obtained in the 90-days and one-year toxicity studies in dogs, and in the developmental toxicity studies of rabbits. FSCJ thus established an acceptable daily intake (ADI) for glyphosate at 1 mg/kg bw/day, applying a safety factor of 100 to the NOAEL. The lowest NOAEL for adverse effects elicited by a single oral administration of glyphosate was 1,000 mg/kg bw observed in an acute toxicity studies in rats and mice. It is thus unnecessary to specify an acute reference dose (ARfD), due to the exceeding of the cut off level (500 mg/kg bw).

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of glyphosate (CAS No. 1071-83-6), an amino acid herbicide, based on results from various studies.

Several technical grades of glyphosate are currently available in Japan. Five-distinct assessment data sets were submitted from each manufacturer. Toxicological profiles were found to be largely consistent among them after the verification individually. The summary of the risk assessment of each technical grade of glyphosate (Glyphosate I to V) is shown in Appendix.

The active ingredient of glyphosate is distributed various salt form such as glyphosate ammonium salt (CAS No. 40465-66-5), glyphosate isopropylamine salt (CAS No. 38641-94-0) and glyphosate potassium salt (CAS No. 70901-12-1). Those salts are soluble in water. Whatever salt are applied to crops, the residue on the crops exists in the form of free acid. FSCJ established the unified acceptable daily intake (ADI) and acute reference dose (ARfD) of glyphosate through compiling these assessment results.

In general, ^{14}C-glyphosate orally administrated rapidly reached to the C_{max} value in plasma and then was eliminated in rats. At least 20% of the radioactivity was absorbed and excreted efficiently in feces. Unchanged glyphosate and aminomethyl phosphonic acid (AMPA) were found in urine and feces.

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The original full report is available in Japanese at http://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20100216003&fileId=201
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The fates of ^{14}C-glyphosate in livestock (goats and chicken) were also examined. Unchanged glyphosate was found as the major radioactive substance in urine, feces, organs and tissues, and AMPA was also found as the minor component.

On the fate of ^{14}C-glyphosate, and isopropylamine, potassium, trimesium or sodium salt of ^{14}C-glyphosate in plants, AMPA was found more than 10% of the total radioactive residue (TRR). *N*-Acetylglyphosate and *N*-acetyl-AMPA were detected in the glyphosate tolerant soybean and corn as more than 10% of TRR.

Major adverse effects of glyphosate were observed on reduced gain of body weight, GI tract (diarrhea, increased cecum weight, bowel dilatation, thickening of intestinal mucosa), and liver (increased alkaline phosphatase (ALP), hepatocellular hypertrophy). Glyphosate had no neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity, and genotoxicity.

Among no-observed-adverse-effect levels (NOAELs) of each technical grade of glyphosate, the lowest value was 75 mg/kg bw/day on Glyphosate I derived from the maternal effects in the developmental toxicity study of rabbits. FSCJ, however, recognized it appropriate to set 100 mg/kg bw/day as the overall NOAEL in the developmental toxicity studies of rabbits, considering the dose settings and the toxicological effects observed in the four other corresponding studies.

As the whole, the lowest value among NOAELs was 100 mg/kg bw/day obtained in the 90-days and one-year toxicity studies in dogs, and in the developmental toxicity studies of rabbits. FSCJ thus established an ADI for glyphosate at 1 mg/kg bw/day, applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for adverse effects elicited by a single oral administration of glyphosate was 1,000 mg/kg bw observed in an acute toxicity studies in rats and mice. It is thus unnecessary to specify an ARfD, due to the exceeding of the cut off level (500 mg/kg bw).

In plants, AMPA, *N*-acetyl-AMPA, and *N*-Acetylglyphosate were observed as exceeded 10% of TRR. *N*-acetyl-AMPA and *N*-Acetylglyphosate were not detected in rats. *N*-acetyl-AMPA had a very low acute toxicity (LD_{50} was beyond 5,000 mg/kg bw), and no genotoxicity. Thus the residue definition for the dietary risk assessment was identified to be glyphosate and *N*-Acetylglyphosate in agricultural products, and glyphosate (parent compound only) in livestock products.

Appendix

Glyphosate I

FSCJ conducted a risk assessment of glyphosate (CAS No. 1071-83-6) [glyphosate ammonium salt (CAS No. 40465-66-5), glyphosate isopropylamine salt (CAS No. 38641-94-0) and glyphosate potassium salt (CAS No. 70901-12-1)], an amino acid herbicide, based on results from various studies.

The data used in the assessment include fate in animals (rats and rabbits), fate in plants (soybeans, grapes and others), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of glyphosate were observed on GI tract (diarrhea, loose feces) and reduced gain of body weight. None of carcinogenicity, reproductive toxicity, teratogenicity and genotoxicity was observed.

Based on the results from various studies, glyphosate (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest NOAEL obtained in all the studies was 75 mg/kg bw/day in a developmental toxicity study in rabbits. FSCJ established ADI of 0.75 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for adverse effects elicited by a single oral administration of glyphosate was 1,000 mg/kg bw obtained in an acute toxicity study in mice. It is thus unnecessary to specify an ARfD, due to the exceeding of the cut off level (500 mg/kg bw).

Glyphosate II

FSCJ conducted a risk assessment of glyphosate (CAS No. 1071-83-6) [glyphosate potassium salt (CAS No. 70901-12-1)], an amino acid herbicide, based on results from various studies.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice, lemon and others), residues in crops, subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), combined chronic toxicity/carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of glyphosate were observed on reduced gain of body weight and liver (increased alanine aminotransferase (ALT) and ALP). None of neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity and genotoxicity of glyphosate was observed.

Based on the results from various studies, glyphosate and N-acetylglyphosate were identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest NOAEL obtained in all the studies was 100 mg/kg bw/day in a developmental toxicity study in rabbits. FSCJ established an ADI of 1 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for adverse effects elicited by a single oral administration of glyphosate was 1,000 mg/kg bw obtained in an acute neurotoxicity study in rats. It is thus unnecessary to specify an ARfD, due to the exceeding of the cut off level (500 mg/kg bw).

Glyphosate III

FSCJ conducted a risk assessment of glyphosate (CAS No. 1071-83-6) [glyphosate isopropylamine salt (CAS No. 38641-94-0)], an amino acid herbicide, based on results from various studies.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice, apple and others), residues in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of glyphosate were observed on GI tract (diarrhea, bowel dilatation, thickening of intestinal mucosa), kidney (nephrosis), liver (increased ALP, hepatocellular hypertrophy), and blood (decreased red blood cell (RBC)). None of neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity, and genotoxicity relevant to human health was observed.

Based on the results from various studies, glyphosate (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest NOAEL obtained in all the studies was 100 mg/kg bw/day in a 90-day subacute toxicity study in rats and in dogs, and in a one-year chronic toxicity study in dogs. FSCJ established an ADI of 1 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for adverse effects elicited by a single oral administration of glyphosate was 5,000 mg/kg bw obtained in an acute toxicity study in rats and mice. It is thus unnecessary to specify an ARfD, due to the exceeding of the cut off level (500 mg/kg bw).

Glyphosate IV

FSCJ conducted a risk assessment of glyphosate (CAS No. 1071-83-6) [glyphosate isopropylamine salt (CAS No. 38641-94-0)], an amino acid herbicide, based on results from various studies.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice, apple and others), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of glyphosate were observed on reduced gain of body weight, GI tract (loose feces, increased cecum weight), and blood (anemia). None of carcinogenicity, reproductive toxicity, teratogenicity and genotoxicity was observed.

Based on the results from various studies, glyphosate (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest NOAEL obtained in all the studies was 100 mg/kg bw/day in a developmental toxicity study in rabbits. FSCJ established an ADI of 1 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for adverse effects elicited by a single oral administration of glyphosate was 5,000 mg/kg bw obtained in an acute toxicity study in rats and mice. It is thus unnecessary to specify an ARfD, due to the exceeding of the cut off level (500 mg/kg bw).

Glyphosate V

FSCJ conducted a risk assessment of glyphosate (CAS No. 1071-83-6) [glyphosate isopropylamine salt (CAS No. 38641-94-0)], an amino acid herbicide, based on results from various studies.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice, apple and others), residues in crops, subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of glyphosate were observed on GI tract (loose feces and diarrhea). None of neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity and genotoxicity was observed.

Based on the results from various studies, glyphosate (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest NOAEL obtained in all the studies was 200 mg/kg bw/day in a developmental toxicity study in rabbits. FSCJ established an ADI of 2 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

No adverse effects elicited by a single oral administration of glyphosate was observed. It is thus unnecessary to specify an ARfD.

Levels relevant to toxicological evaluation of glyphosate

Species	Study	Technical Grade No.	Dose (ppm)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints (Notes)
Rat	90-day toxicity study	I	0, 1,000, 5,000, 20,000[a]	M: 1,270[b] F: 1,620[b]	-	No toxicity
			0, 200, 2,000, 5,000, 12,500[a]	M: 339 F: 339	M: 839 F: 802	M/F: Reduced gain of body weight, etc
		II	0, 1,000, 5,000, 20,000[a]	M: 81.3 F: 90.4	M: 414 F: 447	M/F: Increased ALT, etc
		III	0, 100, 300, 1,000, 3,000[c] (mg/kg bw/day)	M: 100 F: 300	M: 300 F: 1,000	M/F: loose feces, diarrhea, etc
			0, 2,000, 10,000, 50,000[a]	M: 672 F: 736	M: 3,690 F: 3,790	M/F: Hepatocellular hypertrophy, etc
		IV	0, 3,000, 10,000, 30,000[a]	M: 168 F: 195	M: 569 F: 637	M/F: Increased cecum weight, etc
		V	0, 1,000, 10,000, 50,000[a]	M: 79 F: 90	M: 730 F: 844	M/F: Increased ALP, etc
	90-day neurotoxicity study	II	0, 2,000, 8,000, 20,000[a]	M: 617 F: 1,630[b]	M: 1,550 F: -	M: Reduced gain of body weight, etc F: No toxicity (No subacute neurotoxicity)
		III	0, 2,000, 10,000, 50,000[a]	M: 734 F: 858	M: 4,090 F: 5,010	M/F: Diarrhea, etc (No subacute neurotoxicity)
		V	0, 1,000, 5,000, 20,000[a]	M: 1,500[b] F: 1,560[b]	-	M/F: No toxicity (No subacute neurotoxicity)
	One-year toxicity study	II	0, 2,000, 8,000, 20,000[a]	M: 141 F: 167	M: 560 F: 671	M/F: Increased ALT/ALP, etc
	Two-year combined chronic toxicity/ carcinogenicity study	I	0, 2,000, 8,000, 20,000[a]	M: 362 F: 457	M: 940 F: 1,180	M: Cataract like change F: Reduced gain of body weight (Not carcinogenic)
		II	0, 2,000, 6,000, 20,000[a]	M: 121 F: 145	M: 361 F: 437	M/F: Increased ALP/ALT, etc (Not carcinogenic)
		III	0, 500, 4,000, 32,000[a]	M: 201 F: 239	M: 1,750 F: 2,000	M/F: Decreased RBC (Not carcinogenic)
		IV	0, 3,000, 10,000, 30,000[a]	M: 104 F: 115	M: 354 F: 393	M/F: Increased absolute cecum weight, etc (Not carcinogenic)
		V	0, 1,500, 5,000, 15,000[a]	M: 1,080[b] F: 349	M: - F: 1,380	M: No toxicity F: Mineralization of medullary-cortical zone in the kidney (Not carcinogenic)

(continued.)

Species	Study	Technical Grade No.	Dose (ppm)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints (Notes)
Rat (cont'd)	Two-generation of reproductive toxicity study	I	0, 2,000, 10,000, 30,000[a]	PM: 666 PF: 777 F_1M: 711 F_1F: 804	PM: 1,980 PF: 2,320 F_1M: 2,230 F_1F: 2,540	P/F_1: Reduced gain of body weight, etc (No effect on reproduction)
		II	0, 1,000, 3,000, 10,000[a]	Parent PM: 293 PF: 1,050[b] F_1M: 352 F_1F: 1,220[b] Offspring PM: 293 PF: 323 F_1M: 352 F_1F: 371	Parent PM: 985 PF: - F_1M: 1,160 F_1F: - Offspring PM: 293 PF: 1,050 F_1M: 352 F_1F: 1,220	Parent M: Reduced gain of body weight, etc F: No toxicity Offspring M/F: Reduced gain of body weight (No effect on reproduction)
		III	0, 400, 4,000, 40,000[a]	PM: 360 PF: 374 F_1M: 480 F_1F: 465	PM: 3,810 PF: 3,730 F_1M: 5,040 F_1F: 4,860	P/F_1: Reduced gain of body weight, etc (No effect on reproduction)
		IV	0, 1,200, 6,000, 30,000[a]	PM: 417 PF: 485 F_1M: 458 F_1F: 530	PM: 2,150 PF: 2,530 F_1M: 2,410 F_1F: 2,760	P: Loose feces, dilated caecum, etc F_1: Dilated caecum, etc (No effect on reproduction)
		V	0, 1,500, 5,000, 15,000[a]	PM: 959[b] PF: 1,170[b] F_1M: 1,170[b] F_1F: 1,380[b]	PM: - PF: - F_1M: - F_1F: -	P/F_1: No toxicity (No effect on reproduction)
	Developmental toxicity study	I	0, 300,1,000, 3,500[c] (mg/kg bw/day)	Maternal/Fetus: 1,000	Maternal/Fetus: 3,500	Maternal: Increased mortality rate, etc Fetus: Low body weight, etc (Not teratogenic)
		II	0, 250, 500, 1,000[c] (mg/kg bw/day)	Maternal/Fetus: 1,000[b]	Maternal/Fetus: -	No toxicity (Not teratogenic)
		III	0, 250, 500, 1,000[c] (mg/kg bw/day)	Maternal/Fetus: 1,000[b]	Maternal/Fetus: -	No toxicity (Not teratogenic)
		IV	0, 30, 300, 1,000[c] (mg/kg bw/day)	Maternal: 300 Fetus: 1,000[b]	Maternal: 1,000 Fetus: -	Maternal: Loose feces, etc Fetus: No toxicity (Not teratogenic)
		V	0, 100, 500, 1,000[c] (mg/kg bw/day)	Maternal/Fetus: 1,000	Maternal/Fetus: -	No toxicity (Not teratogenic)

(continued.)

Species	Study	Technical Grade No.	Dose (ppm)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints (Notes)
Mouse	90-day toxicity study	I	0, 5,000, 10,000, 50,000[a]	M: 1,870 F: 2,740	M: 9,700 F: 14,800	M/F: Reduced gain of body weight
		III	0, 2,000, 10,000, 50,000[a]	M: 1,630 F: 423	M: 7,990 F: 1,960	M: Loose feces, bloody feces, etc F: Decreased absolute/ relative kidney weight
		IV	0, 5,000, 10,000, 50,000[a]	M: 600 F: 765	M: 1,220 F: 1,490	M/F: Increase trend in cecum weight
	Two-year combined chronic toxicity/ carcinogenicity study	II	0, 100, 1,000, 8,000[a]	M: 118 F: 159	M: 991 F: 1,340	M/F: Reduced gain of body weight (Not carcinogenic)
	18-month carcinogenicity study	I	[2 year] 0, 1,000, 5,000, 30,000[a]	M: 830 F: 979	M: 4,930 F: 6,130	M/F: Reduced gain of body weight (Not carcinogenic)
		III	0, 500, 5,000, 50,000[a]	M: 685 F: 909	M: 7,470 F: 8,690	M/F: Loose feces, etc (Not carcinogenic)
		IV	0, 1,600, 8,000, 40,000[a]	M: 838 F: 153	M: 4,350 F: 787	M: Increased absolute/ relative cecum weight, etc F: Reduced gain of body weight, etc (Not carcinogenic)
		V	0, 500, 1,500, 5,000[a]	M: 810[b] F: 1,080[b]	M: - F: -	No toxicity (Not carcinogenic)
Rabbit	Developmental toxicity study	I	0, 75, 175, 350[c] (mg/kg bw/day)	Maternal: 75 Fetus: 350[b]	Maternal: 175 Fetus: -	Maternal: Diarrhea, loose feces Fetus: No toxicity (Not teratogenic)
		II	0, 100, 175, 300[c] (mg/kg bw/day)	Maternal: 100 Fetus: 175	Maternal: 175 Fetus: 300	Maternal: Reduced gain of body weight, etc Fetus: Low body weight, etc
		III	0, 87.5, 175, 350[c] (mg/kg bw/day)	Maternal/Fetus: 350	Maternal/Fetus: -	No toxicity (Not teratogenic)
		IV	0, 10, 100, 300[c] (mg/kg bw/day)	Maternal: 100 Fetus: 300[b]	Maternal: 300 Fetus: -	Maternal: Loose feces, abortion/premature birth (2 cases), reduce trend in body weight gain Fetus: No toxicity (Not teratogenic)
		V	0, 50, 200, 400[c] (mg/kg bw/day)	Maternal: 200 Fetus: 400[b]	Maternal: 400 Fetus: -	Maternal: Death, diarrhea, reduced gain of body weight, etc Fetus: No toxicity (Not teratogenic)

(continued.)

Species	Study	Technical Grade No.	Dose (ppm)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints (Notes)
Dog	90-day toxicity study	I	[6-month] 0, 10, 60, 300[c] (mg/kg bw/day)	M: 300[b] F: 300[b]	M: - F: -	No toxicity
		II	0, 2,000, 10,000, 50,000[a]	M: 323 F: 334	M: 1,680 F: 1,750	M: Decreased Alb, TP, etc F: Increased ALP
		III	0, 30, 100, 300[c] (mg/kg bw/day)	M: 100 F: 100	M: 300 F: 300	M/F: Reduce gain of body weight, etc
		IV	0, 1,600, 8,000, 40,000[a]	M: 1,020[b] F:1,010[b]	M: - F: -	No toxicity
		V	0, 30, 300, 1,000[c] (mg/kg bw/day)	M: 300 F: 300	M: 1,000 F: 1,000	M/F: Loose watery feces, etc
	One-year toxicity study	I	0, 20, 100, 500[c] (mg/kg bw/day)	M: 500[b] F: 500[b]	M: - F: -	No toxicity
		II	0, 3,000, 15,000, 30,000[a]	M: 907[b] F: 448	M: - F: 926	M: No toxicity F: Reduced gain of body weight
		III	0, 30, 100, 300[c] (mg/kg bw/day)	M: 100 F: 100	M: 300 F: 300	M/F: Diarrhea, bloody feces, etc
		IV	0, 1,600, 8,000, 50,000[a]	M: 182 F: 184	M: 1,200 F: 1,260	M/F: Loose feces, reduce trend in body weight gain, etc
		V	0, 30, 125, 500[c] (mg/kg bw/day)	M: 500[b] F: 500[b]	M: - F: -	No toxicity
Genotoxicity		I	No evidence of genotoxicity			
		II	No evidence of genotoxicity			
		III	No genotoxicity relevant for human health [Pseudo positive in *in vitro* chromosomal aberration test (+S9), but negative in *in vivo* micronucleus test up to the highest dose in accordance with OECD TG.]			
		IV	No evidence of genotoxicity			
		V	No evidence of genotoxicity			

M, Male; F, Female; M/F, both sexes; PM, Male in P (Parent) generation; PF, Female in P generation; F_1M, Male in F_1 generation; F_1F, Female in F_1 generation; -, No effect observed at the highest dose tested; [a], Dietary administration; [b], Highest dose tested; [c], Gavage administration; Alb, Albumin; TP, Total protein.

Absorption, distribution, excretion and metabolism of glyphosate in animals

Kinetics

Dose (mg/kg bw)	1		10				25		100	
Sex	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
T_{max} (hr)	3.9	8	4	1.7	6	3	4	4	2	2
C_{max} (μg/g)	0.016	0.037	0.168	0.413	0.125	0.162	0.29	0.74	5.61	5.94
$T_{1/2}$ (hr)	10.9	8.07					18	12	-	-
α (hr)		-	-				-	-	2.3	2
β (day)		-	-				-	-	-	2.6
AUC	0.257[a] (hr μg/mL)	0.338[a] (hr μg/mL)	245 (min μg/mL)	226 (min μg/mL)			4.6[a] (hr μg/g)	9.5[a] (hr μg/g)	46.9[b] (hr μg/mL)	64.1b (hr μg/mL)
Rate of absorption (%)	28.1–32.5		30.2–36.2		19–30		39.9		22.9–36.2	

/: Not measured; -: Not indicated; [a]: $AUC_{0\text{-}24\ hr}$

Metabolism

In both urine and feces samples, the major radioactive component was unchanged glyphosate (urine: 15.2–31.0% of administrated dose, feces: 67.6–83.0% of administrated dose). Small amounts of aminomethyl phosphonic acid (AMPA), 0.06–0.66% of administrated dose in urine, trace-1.4% of administrated dose in feces) and methyl aminomethyl phosphonic acid (MAMPA) were detected.

Distribution in tissues

Dose (mg/kg bw)	Hours after administration (hrs[a])	Sex	Organ (μg/g)
1	72	Male	Bone (0.123), Gastro-intestinal tract (0.031), Kidney (0.020), Carcass[b] (0.016), Liver (0.012), Others (0.010>)
		Female	Bone (0.112), Gastro-intestinal tract (0.075), Carcass (0.024), Skin (0.014), Liver (0.012), Kidney (0.012), Others (0.010>)
10	72	Male	Bone (0.511), Gastro-intestinal tract (0.152), Kidney (0.068), Carcass (0.062), Liver (0.059), Others (0.05>)
		Female	Bone (0.395), Gastro-intestinal tract (0.152), Carcass (0.056), Kidney (0.049) Liver (0.044), Others (0.03>)
	168	Male	Bone (0.552), Carcass (0.106), Others (0.05>)
		Female	Bone (0.313), Carcass (0.087), Others (0.05>)
		Male	Bone(0.47), Bone marrow(0.044), Kidney(0.035), Carcass (0.034), Gastro-intestinal tract (0.030), Others (0.03>)
		Female	Bone (0.58), Bone marrow (0.093), Gastro-intestinal tract (0.032), Carcass (0.028), Lymph node (0.028), Others (0.025>)
25	120	Male	Bone (1.29), Large intestine (0.555), Carcass (0.294), Liver (0.216), Small intestine (0.206), Kidney (0.202), Others (0.2>)
		Female	Bone (2.31), Stomach (0.796), Liver (0.333), Kidney (0.320), Urinary bladder (0.282), Lung (0.234), Small intestine (0.221), Carcass (0.201), Others (0.2>)
100	168	Male	Liver (0.518), Kidney (0.483), Stomach (0.424), Others (0.4>)
		Female	Stomach (0.600), Kidney (0.440), Liver (0.416), Others (0.4>)

[a], After single oral administration; [b], Remaining without organs/tissues.

Excretion

Dose (mg/kg bw)	1[a]		10[b]		10[a]				25[c]		100[a]	
Sex	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Urine (%)	18.4	27.2	13.3	11.0	28.6	22.5	22.5	19.4	42.9	61.4	55.5	36.2
Feces (%)	72.6	62.4	88.5	88.7	62.4	69.4	74.6	84.3	47.3	32.0	43.5	62.9

Dose (mg/kg bw)	100[a]		250[c]		600[a]		1,000[b]		1,000[a]			
Sex	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Urine (%)	39.4	43.1	42.0	39.9	30.3	29.5	16.8	17.7	17.8	14.3	23.0	22.9
Feces (%)	41.2	42.4	49.2	55.6	74.7	74.2	89.6	84.5	68.9	69.4	75.6	76.6

[a], During 168 hrs after single oral administration; [b], During 72 hrs after single oral administration; [c], During 48 hrs after single oral administration.