CYANTRANILIPROLE

First draft prepared by
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Explanation

Cyantraniliprole is the International Organization for Standardization–approved common name for 3-bromo-1-(3-chloro-2-pyridyl)-4′-cyano-2′-methyl-6′-(methylcarbamoyl)pyrazole-5-carboxanilide (International Union of Pure and Applied Chemistry), with Chemical Abstracts Service No. 736994-63-1. It is a new second-generation ryanodine receptor insecticide whose pesticidal mode of action is through unregulated activation of insect ryanodine receptor channels, which leads to internal calcium store depletion and impaired regulation of muscle contraction, causing paralysis and eventual death of the insect. Cyantraniliprole is used to control insect pests in fruit crops, tree nuts, oil seed crops, cotton, grapes, rice, vegetables, ornamentals and turf around the world.

Cyantraniliprole has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and is being evaluated by the present Meeting at the request of the Codex Committee on Pesticide Residues.

All critical studies were certified as complying with good laboratory practice (GLP).

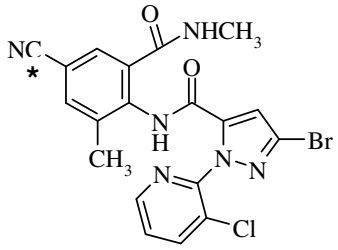
Evaluation for acceptable daily intake

1. Biochemical aspects

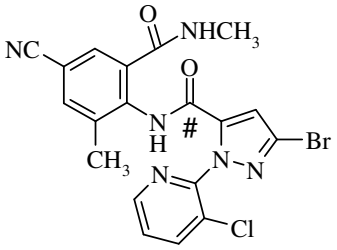
1.1 Absorption, distribution and excretion

The absorption, distribution and excretion of cyantraniliprole in rats following oral administration have been assessed in a quantitative single low-dose and single high-dose material balance study and in a 14-day repeated-dose study. The experiments were performed by dosing rats with [cyano-^{14}C]cyantraniliprole ([CN-^{14}C]cyantraniliprole) (radiochemical purity 99%) and [pyrazole-carbonyl-^{14}C]cyantraniliprole ([PC-^{14}C]cyantraniliprole) (radiochemical purity 98.1–99%), diluted with cyantraniliprole technical (purity 93.4%), either separately (single-dose study) or as a 1 : 1 weight per weight (w/w) mixture (repeated-dose study). The structure of cyantraniliprole used in the metabolism studies and the label positions are given in Fig. 1.

Fig. 1. The chemical structure and the label positions of cyantraniliprole



[CN-^{14}C]cyantraniliprole (cyano label)
* = location of the radiolabel



[PC-^{14}C]cyantraniliprole (pyrazole-carbonyl label)
= location of the radiolabel

(a) Single-dose administration

The absorption, distribution, metabolism and excretion of cyantraniliprole were studied in male and female Sprague-Dawley Crl:CD(SD) rats (four of each sex per group) administered either [CN-^{14}C]cyantraniliprole or [PC-^{14}C]cyantraniliprole. Experiments were performed to study the pharmacokinetic behaviour of radioactive residues in plasma and red blood cells, the disposition and material balance of total ^{14}C residues among tissues and excreta, the percentage and concentration of ^{14}C residues in tissues at selected times after dosing (the time at which the maximum concentration in plasma is reached [T_{max}], $T_{max/2}$ and terminal sacrifice) and the elimination of ^{14}C residues in bile. The profile of metabolites was characterized in urine, faeces and bile (see section 1.2).

All rats received the appropriate levels of radioactivity (MBq/animal) at the targeted dose rates of 10 and 150 mg/kg body weight (bw). The mean radioactivity dose ranged from 0.86 to 1.84 MBq for male rats and from 0.62 to 1.29 MBq for female rats.

The sex-specific kinetics of the two forms of radiolabelled cyantraniliprole were very similar; however, at low and high doses of each label, the peak plasma concentration (C_{max}), half-life ($t_{½}$) and area under the plasma concentration–time curve (AUC) were approximately 2.0- to 2.5-fold higher in female rats than in male rats (Table 1).

Table 1. Kinetic parameters of single-dose treatment of rats with cyantraniliprole at low and high doses

	10 mg/kg bw				150 mg/kg bw			
	[CN-^{14}C]		[PC-^{14}C]		[CN-^{14}C]		[PC-^{14}C]	
	Males	Females	Males	Females	Males	Females	Males	Females
T_{max} (h)	2.0	1.8	2.5	1.6	1.4	2.5	1.0	1.3
C_{max} (µg/g)	6.3	11.5	4.8	10.4	42.2	47.4	42.2	52.2
$t_{½}$ (h)	42.3	129	53.8	117	61.7	64.7	55.3	79.7
AUC (h·µg/g)	195	609	245	638	1 730	3 590	1 830	5 470

AUC: area under the plasma concentration–time curve; bw: body weight; C_{max}: peak plasma concentration; $t_{½}$: half-life; T_{max}: time to reach C_{max}
Source: Gannon (2010a)

Rats with bile duct cannulae were administered both [PC-^{14}C]cyantraniliprole and [CN-^{14}C]cyantraniliprole separately at a dose of either 10 or 150 mg/kg bw to measure the percentage of absorbed oral dose recoverable over 48 hours from bile, urine, carcass and the gastrointestinal tract (excluding contents). There was no significant difference in absorption of the two forms of radiolabelled cyantraniliprole. The mean total recovery (including cage washings) of radioactivity accounted for 89.0–101.6% of the dose. Absorption of the 10 mg/kg bw dose was higher than absorption of the 150 mg/kg bw dose. The percentage recoveries were 75.8–80.4% in male rats and 62.6–74.9% in female rats after the low dose and 38.8–40.0% in male rats and 31.4–32.2% in female rats after the high dose (Table 2) (Gannon, 2010a).

Table 2. Percentage absorption of radioactivity over 48 hours based on biliary elimination and material balance following a 10 or 150 mg/kg bw single oral dose of [CN-^{14}C]cyantraniliprole or [PC-^{14}C]cyantraniliprole

	10 mg/kg bw				150 mg/kg bw			
	[CN-^{14}C]		[PC-^{14}C]		[CN-^{14}C]		[PC-^{14}C]	
	Males	Females	Males	Females	Males	Females	Males	Females
Absorption (%)	75.8	62.6	80.4	74.9	40.0	31.4	38.8	32.2

Source: Gannon (2010a)

The distribution of ^{14}C residues was evaluated as the percentage of the administered dose, concentration of ^{14}C equivalents per gram of tissue and tissue : plasma concentration ratios at T_{max}, $T_{max/2}$ and terminal sacrifice after single oral dose administration. There was no significant difference in tissue distribution between dosing with the [CN-^{14}C]cyantraniliprole or [PC-^{14}C]cyantraniliprole. Most of the dose was initially associated with the gastrointestinal tract contents and subsequently showed uptake and distribution to all tissues, with higher concentrations at the T_{max} (2 hours) in liver, gastrointestinal tract, gastrointestinal tract contents, lungs, pituitary, thyroid, adrenals and urinary bladder. By 168 hours, the concentrations in most organs and tissues were much reduced, with higher concentrations remaining in liver, pituitary, adrenals and thyroid. The percentage recovery and tissue concentration data showed that female rats retained a greater proportion of ^{14}C residues compared with male rats. The reductions in plasma and tissue ^{14}C residue concentrations at high and low doses were generally similar. These observations were consistent with the shorter elimination half-life in male rats compared with female rats. The tissue : plasma concentration ratios were less than or equal to 1 by 168 hours after dose administration. Many of the tissue : plasma concentration ratios were below 1 at the $T_{max/2}$ time point as well.

There was no significant difference in excretion between rats administered [CN-^{14}C]cyantraniliprole or [PC-^{14}C]cyantraniliprole. Rats given a single 10 mg/kg bw dose of either radiolabelled cyantraniliprole compound excreted a greater percentage of the dose in urine compared with rats dosed with 150 mg/kg bw. For both dose levels and labels, most of the dose was excreted by 24–48 hours after administration. The percentage recovery from rats of the 10 mg/kg bw dose level at 168 hours was 22.0–34.6% for urine, 46.8–61.6% for faeces and 1.1–5.4% for tissues. Lower absorption from the gastrointestinal tract occurred in rats given the 150 mg/kg bw dose, as indicated by the lower percentage of the dose in tissues and urine and the greater percentage of the dose excreted in the faeces. For all groups in which material balance was measured, the mean percentage for total recovery by 7 days after dosing ranged from 88.3% to 96.5% (Table 3).

Table 3. Excretion in urine and faeces 168 hours after treatment

	% of total administered radioactivity									
	Single dose								Repeated dose	
	10 mg/kg bw				150 mg/kg bw				10 mg/kg bw	
	[CN-^{14}C]		[PC-^{14}C]		[CN-^{14}C]		[PC-^{14}C]		[CN-^{14}C] + [PC-^{14}C]	
	M	F	M	F	M	F	M	F	M	F
Urine	27.7	22.0	34.6	23.7	14.8	13.2	11.8	12.9	28.8	20.3
Faeces	61.5	61.6	46.8	60.6	77.6	78.6	80.1	77.6	60.8	61.9
Carcass[a]	1.14	4.25	1.67	5.35	0.68	2.45	0.25	2.30	0.8	2.5
Cage washing	5.62	5.35	5.23	3.40	1.66	1.12	2.27	1.08	2.8	4.5
Total[b]	96.5	92.6	88.3	93.0	95.0	95.1	94.5	93.7	93.2	89.1

F: females; M: males

[a] Total of tissues and carcass except erythrocytes and plasma.

[b] The mean percentage for total recovery in individual data.

Source: Gannon (2010a)

(b) Repeated-dose administration

A 1 : 1 w/w mixture of [CN-^{14}C]cyantraniliprole and [PC-^{14}C]cyantraniliprole was administered to groups of three male and three female Sprague-Dawley rats orally by gavage at a dose level of 10 mg/kg bw per day for 14 days. The average daily dose was 10.5 mg/kg bw, corresponding to a radioactivity dose rate of 0.11 MBq/rat per day.

The primary objective of this study was to examine the kinetics of ^{14}C-labelled cyantraniliprole in whole blood, plasma, red blood cells, fat, kidneys, liver and muscle during and following multiple oral dose administration to rats for determination of steady-state kinetics during dose administration and tissue/organ elimination half-lives. The second objective was to establish the metabolite profile in urine and faeces collected for 24 hours after the 1st, 7th and last days of dosing (see section 1.2). The mean body weights during the 14-day dosing period were 297 ± 27 g for males and 203 ± 19 g for females.

Concentration (µg equivalents/g), tissue : plasma ratio and percentage of dose were calculated for tissues collected from male and female rats at various times during and after exposure. In male rats, tissues were collected on day 15 and day 21 (1 day and 7 days after last dose). Tissues were collected from female rats on days 5, 9, 12, 15, 17, 21 and 26. There were more collections from female rats because a previous study had found that systemic availability was higher in females than in males following a single oral gavage dose. Because of the higher frequency of tissue collections from female rats, elimination half-lives could be calculated with greater precision than in males. All tissues were collected from male and female animals on day 15 and day 21, but a more limited set of tissues was collected from female rats on the other collection days.

The data show that the tissue concentrations fall rapidly following the end of dosing. The half-lives ranged from 2.6 days in fat to approximately 6 days in whole blood (Table 4). The lack of accumulation was confirmed by the decreasing concentrations in tissues collected at day 15 and day 21 from both male and female rats. The tissue : plasma ratios were all less than 1 following the end of the dosing period, this being additional evidence for a lack of accumulation in tissues. The cumulative excretion of total radioactivity in urine and faeces was evaluated from day 1 through day 20 as both the percentage of accumulating dose and the percentage of total dose. The accumulating dose in urine, which represents the amount excreted in the urine in a 24-hour period, ranged from 24% to 29% in males and from 13% to 20% in females. The total percentage of dose eliminated in the urine was 29% in male rats and 20% in female rats. The accumulating dose in faeces ranged from 43% to 61% in males and from 42% to 62% in females. The total percentage of dose eliminated in the faeces was 61% in males and 62% in females (Gannon, 2010b).

Table 4. Kinetic parameters of residues in female rats following oral dosing by gavage with ^{14}C-labelled cyantraniliprole at 10 mg/kg bw per day for 14 days

	Plasma	Red blood cells	Total blood	Fat	Liver
T_{max} (day)	15	15	15	15	15
C_{max} (µg/g)	60.1	10.4	30.9	45.0	30.7
$t_{½}$ (day)	5.6	5.4	5.7	2.6	4.0
AUC (day·µg/g)	828	161	463	577	402

AUC: area under the plasma concentration–time curve; C_{max}: peak plasma concentration; $t_{½}$: half-life; T_{max}: time to reach C_{max}
Source: Gannon (2010b)

1.2 Biotransformation

The metabolism of cyantraniliprole was investigated in two studies performed in Sprague-Dawley Crl:CD®(SD)IGS BR rats with a 1 : 1 w/w mixture of [CN-^{14}C]cyantraniliprole (radiochemical purity 99%) and [PC-^{14}C]cyantraniliprole (radiochemical purity 98.1–99%), diluted with cyantraniliprole technical (purity 93.4%). The rats were dosed once by gavage with either 10 or 150 mg/kg bw (four rats of each sex per group) (Gannon, 2010a) or daily for 14 days by gavage at a dose of 10 mg/kg bw per day (three males and three females) (Gannon, 2010b). Metabolites were identified and quantified by radiochromatography and liquid chromatography/mass spectrometry.

The main animal metabolites and degradates of cyantraniliprole are shown in Table 5.

In the single-dose studies, cyantraniliprole was found to be readily hydroxylated to form IN-N7B69 and IN-MYX98, and IN-N7B69 was further metabolized to a glucuronide. Cyantraniliprole underwent ring closure to generate IN-J9Z38, which was in turn hydroxylated to form IN-NBC94, its carboxylic acid and its glucuronide conjugate. IN-MYX98 was also metabolized to the closed-ring metabolite IN-MLA84, which, like IN-NBC94, was further oxidized to a hydroxylated metabolite, a carboxylic acid and the glucuronide of the hydroxyl metabolite. The hydroxylated metabolite IN-MYX98 could be *N*-dealkylated to form IN-HGW87 as well as hydroxylated a second time to form bis-hydroxy cyantraniliprole. Cyantraniliprole was also hydroxylated on the pyridine ring, followed by a ring closure analogous to the conversion of cyantraniliprole to IN-J9Z38. Cyantraniliprole could also be *N*-dealkylated and cleaved at the carbonyl bridge to form IN-DBC80.

Metabolites in urine and faeces during and following multiple dosing were the same as those observed in the single oral dose study (Table 6). In most cases, there was very little difference observed between metabolite distribution on day 1, 7 or 14 in urine. In urine from male rats, IN-N7B69 was present at approximately 5% of the dose on day 1 and day 7, but was not detected on day 14. It was not detected on any day in female rat urine. IN-MYX98 was present at only 0.5% of the

administered dose in male urine on day 1, but was present at significantly higher levels by day 7 (5% of the dose) and day 14 (3% of the dose). In contrast, this same metabolite in urine of female rats was present at 7% on day 1, 11% on day 7, but only 1% on day 14. Cyantraniliprole constituted approximately 5% of the dose in female rat urine on days 1 and 7, but was not detected on day 14. IN-MLA84 made up less than 11% of the dose on days 2 and 7, but was 14% of the dose on day 14. The most notable differences in faecal metabolite profile both occurred in the female rat samples. There was an increase in both IN-MLA84 (day 1, 1% of the dose; day 14, 5% of the dose) and IN-MYX98 (day 1, 10% of the dose; day 14, 16% of the dose) as a percentage of the dose (Gannon, 2010a,b).

Table 5. Main metabolites and/or degradates of cyantraniliprole

Codes	Names
Bis-hydroxy cyantraniliprole	3-Bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-(hydroxymethyl)-6-[[(hydroxymethyl)amino]carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide
IN-DBC80	3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxylic acid
IN-F6L99	3-Bromo-*N*-methyl-1*H*-pyrazole-5-carboxamide
IN-HGW87	*N*-[2-(Aminocarbonyl)-4-cyano-6-methylphenyl]-3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide
IN-J9Z38	2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-3,4-dihydro-3,8-dimethyl-4-oxo-6-quinazolinecarbonitrile
IN-JSE76	4-[[[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-3-methyl-5-[(methylamino)carbonyl]benzoic acid
IN-MLA84	2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-1,4-dihydro-8-methyl-4-oxo-6-quinazolinecarbonitrile
IN-MLA84 carboxylic acid	2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-6-cyano-1,4-dihydro-4-oxo-8-quinazolinecarboxylic acid
Hydroxy-IN-MLA84	2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-3,4-dihydro-8-(hydroxymethyl)-4-oxo-6-quinazolinecarbonitrile
Hydroxy-IN-MLA84 glucoside	2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-8-[(β-D-glucopyranosyloxy)-methyl]-1,4-dihydro-4-oxo-6-quinazolinecarbonitrile
Hydroxy-IN-MLA84 glucuronide	[2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-6-cyano-1,4-dihydro-4-oxo-8-quinazolinyl]methyl β-D-glucopyranosiduronate
IN-MYX98	3-Bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2[[(hydroxymethyl)amino]carbonyl]-6-methylphenyl]-1*H*-pyrazole-5-carboxamide
IN-N5M09	6-Chloro-4-methyl-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-2-carbonitrile
IN-N7B69	3-Bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-(hydroxymethyl)-6-[(methylamino)-carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide
IN-N7B69 glucuronide	3-Bromo-1-(3-chloropyridine-2-yl)-*N*-[4-cyano-2-(hydroxymethyl)-6-(methylcarbamoyl)phenyl]-1*H*-pyrazole-6-methyl β-D-*O*-hexopyranosiduronate
IN-NBC94	2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-yl]-3,4-dihydro-8-(hydroxymethyl)-3-methyl-4-oxo-6-quinazolinecarbonitrile
IN-NBC94 glucuronide	2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-yl]-6-cyano-3,4-dihydro-3-methyl-4-oxo-8-quinazolynyl]methyl 8-D-glucopyranosiduronate
IN-PLT97	2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-1,4-dihydro-8-methyl-4-oxo-6-quinazolinecarboxylic acid

Source: Gannon (2010a,b)

Table 6. Metabolites in bile, urine or faeces in single or repeated exposure to cyantraniliprole in rats[a]

Dose (mg/kg bw)	Sex	Sample	% of total administered radioactivity	
			Parent	Metabolites (> 1.0)
Single exposure				
[CN-^{14}C]				
10	M	Urine	0.33	IN-MYX98 (4.52), IN-N7B69 (4.43), bis-hydroxy cyantraniliprole (1.40)
		Faeces	5.06	IN-MYX98 (10.5), bis-hydroxy cyantraniliprole (8.12), IN-N7B69 (4.91), IN-NBC94 (2.41), IN-HGW87 (2.14), IN-MLA84 (1.19)
		Bile	—	IN-NBC94 glucuronide (4.78), IN-N7B69 glucuronide (4.00), hydroxy-IN-MLA84 glucuronide (2.15)
	F	Urine	5.42	IN-MYX98 (11.5)
		Faeces	16.8	IN-MYX98 (14.4), IN-HGW87 (4.10), IN-MLA84 (3.36), IN-NBC94 (3.03), IN-J9Z38 (2.79), IN-N7B69 (2.40), bis-hydroxy cyantraniliprole (2.04)
		Bile	—	IN-NBC94 glucuronide (4.83), IN-N7B69 glucuronide (2.93)
150	M	Urine	1.37	IN-N7B69 (4.53), IN-MYX98 (4.34)
		Faeces	55.8	IN-MYX98 (5.46), bis-hydroxy cyantraniliprole (2.45), IN-N7B69 (1.96), IN-HGW87 (1.14)
		Bile	—	IN-NBC94 glucuronide (3.58), hydroxy-IN-MLA84 glucuronide (1.57), IN-N7B69 glucuronide (1.27)
	F	Urine	1.83	IN-MYX98 (4.88)
		Faeces	55.0	IN-MYX98 (6.73), IN-HGW87 (3.05), IN-MLA84 (2.17), bis-hydroxy cyantraniliprole (1.04)
		Bile	—	IN-NBC94 glucuronide (2.18), IN-N7B69 glucuronide (1.67)
[PC-^{14}C]				
10	M	Urine	1.09	IN-N7B69 (13.6), IN-MYX98 (4.07), bis-hydroxy cyantraniliprole (3.04), IN-DBC80 (2.10)
		Faeces	5.38	IN-MYX98 (9.25), bis-hydroxy cyantraniliprole (5.59), IN-DBC80 (5.30), IN-N7B69 (3.58), IN-NBC94 (2.57), IN-HGW87 (1.46)
		Bile	—	IN-NBC94 (3.41), IN-N7B69 glucuronide (2.78), IN-NBC94 glucuronide (2.62)
	F	Urine	3.58	IN-MYX98 (8.55), IN-N7B69 (1.74)
		Faeces	15.0	IN-MYX98 (17.2), IN-HGW87 (5.52), IN-NBC94 (2.94), IN-MLA84 (2.93), IN-J9Z38 (2.83), IN-DBC80 (2.56), IN-N7B69 (1.96), bis-hydroxy cyantraniliprole (1.93)
		Bile	—	IN-NBC94 glucuronide (3.73), IN-N7B69 glucuronide (3.60), hydroxy-IN-MLA84 glucuronide (2.22), IN-MLA84 (1.55)
150	M	Urine	0.77	IN-N7B69 (3.97), IN-MYX98 (2.10), bis-hydroxy cyantraniliprole (1.08)
		Faeces	65.6	IN-MYX98 (3.59), bis-hydroxy cyantraniliprole (1.64), IN-HGW87 (1.28)
		Bile	—	IN-NBC94 glucuronide (2.25), hydroxy-IN-MLA84 glucuronide (1.15), IN-N7B69 glucuronide (1.07)
	F	Urine	1.35	IN-MYX98 (3.95), IN-MLA84 (1.28), IN-N7B69 (1.21)
		Faeces	59.4	IN-MYX98 (6.37), IN-HGW87 (2.26), IN-MLA84 (2.18), IN-NBC94 (1.08)
		Bile	—	IN-NBC94 glucuronide (2.08), IN-N7B69 glucuronide (1.93), IN-NBC94 (1.21)

Table 6 (continued)

Dose (mg/kg bw)	Sex	Sample	% of total administered radioactivity	
			Parent	Metabolites (> 1.0)
Repeated exposure				
[CN-^{14}C] + [PC-^{14}C]				
10	M	Urine	—	IN-NBC94 (7.95), IN-DBC80 (6.36), IN-MYX98 (3.29), IN-MLA84 (1.91), IN-NBC94 glucuronide (1.48)
		Faeces	9.84	IN-MYX98 (10.7), bis-hydroxy cyantraniliprole (4.55), IN-N7B69 (4.04), IN-NBC94 (3.13), IN-DBC80 (2.27), IN-MLA84 (1.57), IN-HGW87 (1.10)
	F	Urine	—	IN-MLA84 (14.3), IN-DBC80 (1.52), IN-NBC94 (1.30), IN-MYX98 (1.19)
		Faeces	13.5	IN-MYX98 (16.4), IN-MLA84 (5.12), IN-N7B69 (3.65), IN-NBC94 (3.41), IN-HGW87 (2.14), IN-J9Z38 (1.80)

F: female; M: male

[a] Measured 48 and 72 hours after dosing in males and females, respectively.

Source: Gannon (2010a,b)

Analyses for cyantraniliprole and four of its metabolites (IN-J9Z38, IN-MYX98, IN-MLA84 and IN-N7B69) were conducted on plasma samples collected at around test day 60 during the course of 90-day oral toxicity studies in rats (Gannon, 2011b) and mice (Gannon, 2011a) and during 90-day and 1-year (at week 39) oral toxicity studies in dogs (Gannon, 2009; Mawn, 2010). The plasma concentrations of cyantraniliprole and its metabolites in mice, rats and dogs are shown in Table 7.

In mice, IN-MLA84 was by far the most prevalent analyte, and its concentrations were similar in males and females (approximately 400 000 ng/mL) in the highest dietary dose group of 7000 parts per million (ppm) (Table 7). The mean plasma concentrations of cyantraniliprole at this exposure were approximately 4000 ng/mL in male mice and 9000 ng/mL in female mice. All other analytes were present at concentrations less than 800 ng/mL at all dose concentrations. The plasma concentration dose–response curves for IN-MLA84 in particular showed little increase with dose above 300 ppm (Gannon, 2011a).

In rats, the concentration of each analyte was higher in females than in males at all dietary levels, except for IN-J9Z38 at 20 000 ppm, at which concentrations were similar in both males and females (Table 7). In all cases, the most abundant analyte present was IN-MLA84. In the 20 000 ppm dietary group of rats, the mean plasma concentration of IN-MLA84 was 145 890 ng/mL in males and 259 500 ng/mL in females. The parent compound, cyantraniliprole, was the next most abundant analyte, at the very much lower concentrations of 4634 ng/mL in males and 5624 ng/mL in females of the same dietary group. Although these plasma concentrations are quoted for the 20 000 ppm group, there was little increase for any of the analytes compared with the 400 ppm group (Gannon, 2011b).

In contrast to the rats and mice, cyantraniliprole was by far the most abundant analyte in the 90-day dog study; the concentrations were approximately 50 000 ng/mL in both males and females of the 10 000 ppm dietary group. The similarity of cyantraniliprole concentrations in males and females was maintained in all but the lowest (30 ppm) dietary group, where the plasma concentration was approximately 1.5 times higher in females than in males. Concentrations of metabolites IN-J9Z38, IN-MYX98 and IN-N7B69 were not significantly different from each other in females of the high-dose group (10 000 ppm). The concentrations of IN-J9Z38 were similar in males and females. The plasma concentrations of IN-N7B69 and IN-MYX98 were higher in males than in females. The concentrations of the analytes did not increase linearly with dietary concentration in dogs above about 100 ppm (Gannon, 2009). At week 39 of the 1-year dog study, there were no appreciable sex differences in cyantraniliprole concentrations in plasma (Table 7) (Gannon, 2009, 2011a,b; Mawn, 2010).

Table 7. Plasma concentrations of cyantraniliprole and metabolites in mice, rats and dogs

	Plasma concentrations (ng/mL)									
	Males					Females				
Mice in 90-day oral toxicity study	0 ppm	50 ppm	300 ppm	1 000 ppm	7 000 ppm	0 ppm	50 ppm	300 ppm	1 000 ppm	7 000 ppm
Cyantraniliprole	< LOQ	85 ± 33	815 ± 270	1 451 ± 321	3 942 ± 1 045	< LOQ	140 ± 108	1 002 ± 230	2 634 ± 1 073	8 980 ± 9 857
IN-J9Z38	< LOQ	< LOQ	64 ± 18	118 ± 17	278 ± 45	< LOQ	< LOQ	63 ± 24	182 ± 77	312 ± 73
IN-MYX98	< LOQ	26 ± 4	179 ± 29	308 ± 75	839 ± 197	< LOQ	36 ± 16	132 ± 25	334 ± 113	769 ± 147
IN-MLA84	241 ± 76	111 500 ± 11 385	394 100 ± 27 898	402 800 ± 33 320	411 000 ± 34 943	350 ± 87	153 200 ± 16 243	321 200 ± 33 626	502 600 ± 30 146	384 600 ± 108 475
IN-N7B69	< LOQ	< LOQ	68 ± 14	121 ± 29	262 ± 51	< LOQ	< LOQ	59 ± 10	146 ± 39	331 ± 26
Rats in 90-day oral toxicity study	0 ppm	100 ppm	400 ppm	3 000 ppm	20 000 ppm	0 ppm	100 ppm	400 ppm	3 000 ppm	20 000 ppm
Cyantraniliprole	14 ± 4	357 ± 64	1 729 ± 754	3 402 ± 552	4 634 ± 761	< LOQ	1 592 ± 399	4 245 ± 1 232	6 010 ± 1 717	5 624 ± 1 679
IN-J9Z38	< LOQ	173 ± 77	598 ± 195	1 298 ± 590	1 464 ± 304	< LOQ	710 ± 212	1 822 ± 409	1 482 ± 408	1 311 ± 336
IN-MYX98	< LOQ	29 ± 15	110 ± 26	207 ± 70	455 ± 102	< LOQ	108 ± 16	328 ± 83	573 ± 159	716 ± 216
IN-MLA84	< LOQ	16 303 ± 5 758	67 500 ± 13 216	91 605 ± 21 906	145 890 ± 30 076	32 ± 26	29 150 ± 6 457	175 300 ± 40 795	256 800 ± 44 694	259 500 ± 54 056
IN-N7B69	< LOQ	16 ± 4	21 ± 9	35 ± 20	50 ± 25	< LOQ	< LOQ	70 ± 17	137 ± 33	164 ± 35

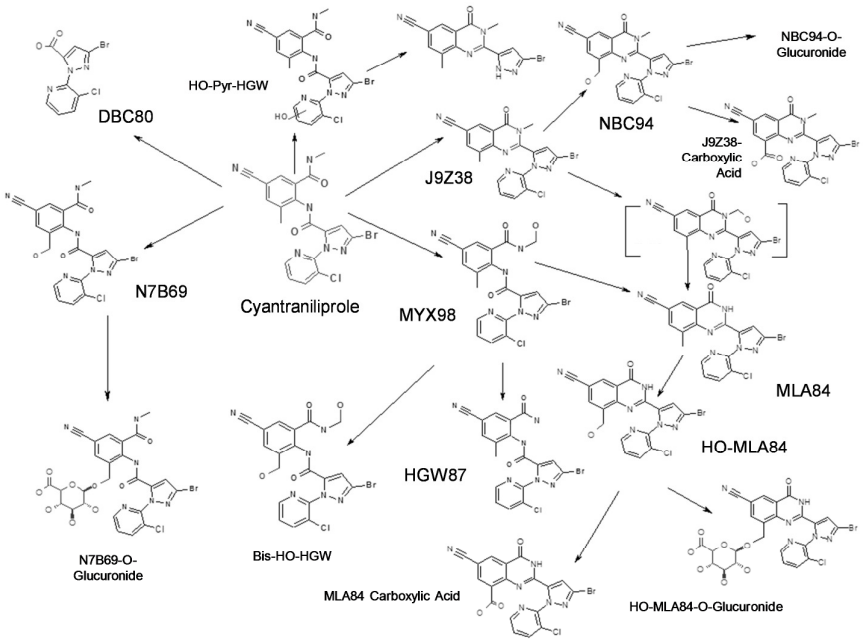
Table 7 (continued)

	Plasma concentrations (ng/mL)							
	Males				Females			
Dogs in 90-day oral toxicity study	30 ppm	100 ppm	1 000 ppm	10 000 ppm	30 ppm	100 ppm	1 000 ppm	10 000 ppm
Cyantraniliprole	1 743 ± 1 110	16 806 ± 6 046	30 963 ± 6 988	51 900 ± 6 597	2 424 ± 1 087	20 600 ± 10 772	28 383 ± 18 056	51 263 ± 26 885
IN-J9Z38	181 ± 61	562 ± 185	1 486 ± 97	2 668 ± 1 205	96 ± 28	661 ± 491	1 176 ± 565	2 043 ± 488
IN-MYX98	256 ± 93	718 ± 159	8 713 ± 2 250	18 717 ± 7 877	77 ± 23	1 021 ± 1 123	1 766 ± 1 070	4 048 ± 895
IN-MLA84	32 ± 7	83 ± 82	217 ± 56	359 ± 183	< LOQ	105 ± 93	158 ± 87	567 ± 255
IN-N7B69	252 ± 154	798 ± 427	11 676 ± 8 501	8 558 ± 8 568	81 ± 21	946 ± 1 402	2 543 ± 1 992	3 801 ± 1 978
Dogs at week 39 in 1-year oral toxicity study	0	5 000	5 000 + recovery		0	5 000	5 000 + recovery	
Cyantraniliprole	< LOQ	62 200	19.7		< LOQ	565	10.8	

LOQ: limit of quantification (5.00 ng/mL)
Source: Gannon (2009, 2011a,b); Mawn (2010)

Proposed pathways for the metabolism of cyantraniliprole in rats are shown in Fig. 2.

Fig. 2. Proposed metabolic pathway of cyantraniliprole in rats



2. Toxicological studies

2.1 Acute toxicity

(a) Lethal doses

The acute toxicities of cyantraniliprole are summarized in Table 8.

Table 8. Summary of acute toxicity of cyantraniliprole

Route	Species and sex	LD_{50} (mg/kg bw)		Abnormalities	Reference
		Males	Females		
Gavage (purity 97.0%; batch no. 9182-1)	SD rat Female (3/group)	—	> 5 000	No treatment-related changes were observed	Carpenter (2009a)
Oral (purity 94.5%; batch no. HGW86-230)	ICR mice Female (5/group)	—	> 5 000	No deaths or abnormal clinical signs	Carpenter (2008a)
Dermal (purity 94.5%; batch no. HGW86-230)	SD rat Male/female (5/sex/group)	> 5 000	> 5 000	No deaths or abnormal clinical signs	Carpenter (2008b)
Inhalation (purity 94.5%; batch no. HGW86-230)	SD rat Male/female (5/sex/group)	> 5.2 mg/L[a]	> 5.2 mg/L[a]	No deaths or abnormal clinical signs	Weinberg (2009)

LD_{50}: median lethal dose

[a] Median lethal concentration (LC_{50}).

(b) Dermal irritation

Cyantraniliprole (purity 97.0%; batch no. HGW86-412) was applied as a single 0.5 g dermal dose to the shaved intact skin of three young adult male New Zealand White rabbits. No dermal irritation was observed (Carpenter, 2009b).

(c) Ocular irritation

A single dose of 62 mg (equivalent to 0.1 mL) of cyantraniliprole (purity 97.0%; batch no. 9182-1) was administered into the lower conjunctival sac of the right eye of three young adult male New Zealand White rabbits. Cyantraniliprole was not irritating to rabbit eyes (Carpenter, 2009c).

(d) Dermal sensitization

The potential of cyantraniliprole (purity 97.0%; batch no. 9182-1) to produce a sensitization response in mice using the local lymph node assay (LLNA) was evaluated. Cyantraniliprole did not produce a sensitization response in mice (Hoban, 2009a).

The dermal sensitization potential of cyantraniliprole (purity 95.6%; lot no. D100487-104; batch no. HGW86-648) was evaluated by the Magnusson-Kligman maximization method in female Hartley albino guinea-pigs. Cyantraniliprole did not produce a dermal sensitization response in guinea-pigs (Nomura, 2011).

Under the conditions of these studies, cyantraniliprole was not a skin sensitizer.

2.2 Short-term studies of toxicity

(a) Oral administration

Mice

In a 28-day feeding study, cyantraniliprole (purity 92.7%; batch no. HWG86-085) was administered to male and female Crl:CD1®(ICR) mice (10 animals of each sex per group) at a concentration of 0, 300, 1000, 3000 or 7000 ppm (equal to 0, 53, 175, 528 and 1261 mg/kg bw per day for males and 0, 63, 212, 664 and 1476 mg/kg bw per day for females, respectively). Parameters evaluated in all mice included body weight, body weight gain, feed consumption, feed efficiency, clinical signs, gross pathology, organ weights, haematology, plasma total protein and microscopic pathology. Cytochrome P450 and β-oxidation in the liver were evaluated. This study was not conducted in accordance with GLP.

No treatment-related deaths or treatment-related changes in clinical observations, body weights, feed intakes, haematology, plasma total protein, organ weights or histopathology were observed. Increased liver weight in males at 3000 ppm and above and in females at 300 ppm and above were considered to be adaptive effects related to induction of drug metabolism enzymes in the liver and not biologically adverse. Cyantraniliprole did not induce hepatic β-oxidation in male or female mice. In male mice, the hepatic total cytochrome P450 (CYP) content was significantly increased at dietary concentrations of 3000 and 7000 ppm. In female mice, total cytochrome P450 content was significantly increased at 300 ppm and higher.

The no-observed-adverse-effect level (NOAEL) for 28-day oral toxicity in mice was 7000 ppm (equal to 1261 mg/kg bw per day), the highest dose tested, based on no adverse effects detected in this study (Carpenter, 2009d).

Cyantraniliprole (purity 93.4%; batch no. HGW86-141) was administered to male and female Crl:CD1®(ICR) mice (10 mice of each sex per group) at a dietary concentration of 0, 50, 300, 1000 or 7000 ppm (equal to 0, 7.2, 47.1, 150 and 1092 mg/kg bw per day for males and 0, 9.7, 58.1, 204 and 1344 mg/kg bw per day for females, respectively) for at least 90 days (97 days for males; 98 days for females). Parameters evaluated included body weight, body weight gain, feed consumption, feed efficiency, clinical signs, haematology, clinical chemistry, ophthalmology, organ weights, and gross

and microscopic pathology. Satellite groups of the same strain of mice (five of each sex per group) were treated similarly for 63 days (non-fasted) to measure plasma concentrations of cyantraniliprole and selected metabolites. The results are shown in Table 7.

No treatment-related deaths occurred, and there were no clinical signs or ophthalmological observations attributable to treatment. No test substance–related effects on body weight or any nutritional parameters were observed. There were no treatment-related changes in clinical pathology parameters (haematology and plasma total protein). A test substance–related increase in liver weights was observed in males at 7000 ppm and in females at 1000 ppm. The increased liver weights correlated with centrilobular hypertrophy of hepatocytes at the same concentrations (Table 9). Both the liver weight increases and the hepatocellular hypertrophy were considered indicative of non-adverse hepatic enzyme induction. Minimal focal necrosis of hepatocytes was increased in females at 7000 ppm. In addition, microscopic examination revealed an increase in mild to slight microvesiculation in fascicular zone cells of adrenal cortex in males fed at 50 ppm and above. The increase in microvesiculation in the adrenal in males was considered to be a non-adverse change within normal physiological limits, because the changes were slight, there was no clear dose dependency and there was no indication of cytotoxicity in organelles by electron microscopic examination. In addition, a lack of increase was detected in a long-term study in mice (Craig, 2011b). Basal urinary corticosterone was comparable between the control and treated groups.

Table 9. Summary of liver effects in a 90-day oral toxicity study in mice

	Males					Females				
	0 ppm	50 ppm	300 ppm	1 000 ppm	7 000 ppm	0 ppm	50 ppm	300 ppm	1 000 ppm	7 000 ppm
No. of rats examined	10	10	10	9	10	10	10	9	10	10
Relative liver weight (% of body weight × 100)	4.800	4.770	5.108	5.209	6.071*	4.912	4.739	4.937	5.449	6.074*
Liver										
Centrilobular hypertrophy of hepatocytes	0	0	0	0	2	0	0	0	1	9
Hepatocellular necrosis, focal	0	0	0	1	1	0	0	1	1	4
Adrenal										
Increased microvesiculation in fascicular zone	0	3	5	4	7	0	0	0	0	0
- Minimal	0	2	2	2	6	0	0	0	0	0
- Slight	0	1	3	2	1	0	0	0	0	0

Source: MacKenzie (2007)

The NOAEL for the 90-day oral toxicity study in mice was 1000 ppm (equal to 204 mg/kg bw per day), based on minimal necrosis in the liver at 7000 ppm (equal to 1344 mg/kg bw per day) in females (MacKenzie, 2007; Gannon, 2011a).

Rats

In a 14-day gavage study, cyantraniliprole (purity 100%; batch no. HGW86-014) was administered to male and female Crl:CD®(SD) IGS BR rats at a dose of 0 (5 males, 5 females), 25 (23 males, 5 females), 300 (23 males, 5 females) or 1000 mg/kg bw per day (8 males, 5 females). For each concentration, the first five males and five females were designated for evaluation of subacute

toxicity and in vivo micronucleus studies (main study group). At the 25, 300 and 1000 mg/kg bw dose levels, the remaining males were designated for pharmacokinetic evaluation. A separate group of five males and five females each received a single 2000 mg/kg bw dose for evaluation of genetic toxicology. Parameters evaluated in the main study group included body weight, clinical signs, clinical chemistry, haematology, urine analysis, macroscopic and microscopic pathology, organ weights, hepatic biochemistry (cytochrome P450, β-oxidation), thyroid hormone levels and genetic toxicology.

No treatment-related changes were observed in the parameters examined except for increases in relative liver and adrenal weights in females at 1000 mg/kg bw per day. The weight increases were not accompanied by any microscopic changes. No significant effects on the thyroid hormones thyroid stimulating hormone (TSH), triiodothyronine (T_3) or thyroxine (T_4) were detected at any dose level. Total cytochrome P450 content in the liver of male or female rats was minimally elevated at 1000 mg/kg bw per day. Cytochrome P450 isozymes of CYP2B1 and CYP1A1 were induced in the liver of both sexes and of males, respectively. Cyantraniliprole did not induce β-oxidation (Nabb, 2010).

In a 28-day feeding study, cyantraniliprole (purity 92.7%; batch no. HGW86D008A) was administered to male and female Crl:CD®(SD) rats (five animals of each sex per group) at a concentration of 0, 600, 2000, 6000 or 20 000 ppm (equal to 0, 53, 175, 528 and 1776 mg/kg bw per day for males and 0, 62, 188, 595 and 1953 mg/kg bw per day for females, respectively). Parameters evaluated included body weight, body weight gain, feed consumption, feed efficiency, clinical signs, ophthalmology, gross pathology, histopathology, organ weights, haematology, clinical chemistry and hepatic biochemical measurements (cytochrome P450, β-oxidation, uridine diphosphate–glucuronyl-transferase [UDPGT]).

No deaths and no clinical or ophthalmological observations were attributable to the treatment. No treatment-related effects on body weight or feed intake were observed. There were no adverse effects on blood chemistry or on gross pathology. In haematological examination, increased degrees of change in erythrocyte shape (e.g. echinocytes and acanthocytes) were observed in males and females at 6000 and 20 000 ppm, without any changes in other red cell parameters. Echinocyte is a common in vitro artefactual finding of red blood cells, and the red cells of Sprague-Dawley rats are especially susceptible to this artefact as a result of in vitro crenation (Reagan, Irizarry & DeNicola, 2008). Therefore, the morphological changes of erythrocytes were not considered adverse.

Liver weights were statistically significantly increased in both sexes fed 6000 ppm and higher. Microscopically, centrilobular hepatocellular hypertrophy was observed in male and female rats at 2000 ppm or higher (Table 10). Thyroid weight increases were detected in both sexes at 6000 ppm and above, and follicular cell hypertrophy in the thyroid was observed in males and females at 2000 ppm and higher. The increase of thyroid follicular cell hypertrophy is considered to be indicative of altered homeostasis in the thyroid.

Hepatic UDPGT activity was slightly induced in both sexes, whereas the effect on induction of cytochrome P450 content was slight (Table 11). Cyantraniliprole did not induce hepatic β-oxidation, a measure of peroxisome proliferation, in male or female rats.

The NOAEL for the 28-day oral toxicity study in rats was 600 ppm (equal to 53 mg/kg bw per day), based on liver hypertrophy and thyroid follicular cell hypertrophy observed in both sexes at 2000 ppm (equal to 175 mg/kg bw per day) (Carpenter, 2009e).

In a 90-day feeding study, cyantraniliprole (purity 93.4%; batch no. HGW86-141) was administered to male and female Crl:CD®(SD) rats (10 of each sex per group) at a dietary concentration of 0, 100, 400, 3000 or 20 000 ppm (equal to 0, 5.7, 22, 168 and 1147 mg/kg bw per day for males and 0, 6.9, 27, 202 and 1346 mg/kg bw per day for females, respectively). Parameters evaluated included body weight, body weight gain, feed consumption, feed efficiency, clinical signs,

haematology, clinical chemistry, urine analysis, ophthalmology, organ weights, and gross and microscopic

Table 10. Select data on organ weights and histopathology in a 28-day oral toxicity study in rats

	0 ppm	600 ppm	2 000 ppm	6 000 ppm	20 000 ppm
Liver weight					
Males					
Absolute liver weight (g)	10.7	11.8	12.1	13.7a	13.7a
Relative[a] liver weight (%)	3.3	3.5	3.9	4.2b	4.4b
Females					
Absolute liver weight (g)	7.7	7.8	9.1	9.5	10.6a
Relative[a] liver weight (%)	3.7	4.0	4.4	4.5b	5.2b
Thyroid weight					
Males					
Absolute thyroid weight (g)	0.017	0.021	0.021	0.024a	0.020
Relative[a] thyroid weight (%)	0.005	0.006	0.007	0.007a	0.006
Females					
Absolute thyroid weight (g)	0.013	0.016	0.016	0.018a	0.022a
Relative[a] thyroid weight (%)	0.006	0.008	0.008	0.008	0.011a
Histopathology					
Males					
Liver: Hepatocellular hypertrophy, centrilobular	0/5	1/5	3/5	5/5	5/5
Thyroid: Follicular cell hypertrophy	0/5	1/5	3/5	3/5	4/5
Females					
Liver: Hepatocellular hypertrophy, centrilobular	0/5	1/5	4/5	3/5	5/5
Thyroid: Follicular cell hypertrophy	05	0/5	1/5	1/5	4/5

a, pair-wise test (Dunnett/Tamhane-Dunnett) significant at $P < 0.05$; b, non-parametric comparison with control (Dunn's) significant at $P < 0.05$

[a] Relative to body weight.

Source: Carpenter (2009e)

Table 11. Summary of hepatic β-oxidation, cytochrome P450 content and UDPGT activity of the liver in a 28-day oral toxicity study in rats

	0 ppm	600 ppm	2 000 ppm	6 000 ppm	20 000 ppm
Males					
β-oxidation activity (nmol/mg protein)	11.3 ± 1.1	9.2 ± 1.8	10.9 ± 2.4	9.4 ± 3.5	9.0 ± 1.1
Cytochrome P450 content (nmol/mg protein)	1.03 ± 0.32	1.05 ± 0.58	1.05 ± 0.58	1.05 ± 0.16	1.30 ± 0.35
UDPGT activity (nmol/mg protein)	9.6 ± 2.3	13.3 ± 5.5	16.0 ± 2.2*	23.5 ± 3.4*	22.3 ± 3.6*
Females					
β-oxidation activity (nmol/mg protein)	15.2 ± 3.1	13.0 ± 3.1	15.4 ± 4.0	17.2 ± 2.2	15.0 ± 2.5
Cytochrome P450 content (nmol/mg protein)	0.50 ± 0.08	0.68 ± 0.24	0.67 ± 0.05[a]	0.76 ± 0.08*	0.76 ± 0.11*
UDPGT activity (nmol/mg protein)	12.3 ± 3.0	16.8 ± 4.8	16.3 ± 3.8	17.5 ± 2.9	17.0 ± 2.9

UDPGT: uridine diphosphate–glucuronosyltransferase; *: $P < 0.05$ (Dunn's test)

[a] $n = 4$.

Source: Carpenter (2009e)

pathology. Five satellite groups of the same strain of rats (five of each sex per group) were administered the same dietary doses for 29 days (males) or 30 days (females). Serum thyroid hormone concentrations and hepatic biochemical parameters (cytochrome P450 and UDPGT) were evaluated using the satellite groups and main group at termination. Blood (from non-fasted animals) was collected on test days 63 (males) and 64 (females) for analysis of the concentration of the test substance and metabolites in plasma. The results are shown in Table 7.

No treatment-related deaths occurred, and there were no clinical signs or ophthalmological observations attributable to treatment. No test substance–related deaths and no clinical or ophthalmological observations were attributed to exposure to the test substance. No treatment-related effects on body weight or feed intake were observed. In haematology, the degree of shape change in erythrocytes (echinocytes and acanthocytes) was increased in both sexes at 3000 and 20 000 ppm, but there was a lack of abnormalities in other haematological parameters. The morphological changes in red blood cells were not considered adverse because they were not associated with changes in other haematological parameters, including red cell mass (see the interpretation of these changes in the 28-day oral toxicity study in rats described above). In blood biochemistry, an increase in cholesterol level (135% of control) and a decrease in triglyceride level (61% of control) were observed in females at 20 000 ppm at termination. Decreases in bilirubin levels in both sexes of all treated groups appeared to be the consequence of an adaptive change involving bilirubin metabolism in the liver. Slight decreases in albumin level in females and in urea level in males at 20 000 ppm at 30 days were not considered to be treatment related due to the absence of these changes at 90 days. In the liver, UDPGT activity was significantly increased in both sexes at 29/30 days, in females at 90 days at 400, 3000 and 20 000 ppm and in males at terminal kill at 20 000 ppm (Table 12). Total cytochrome P450 was slightly increased after 29 days only in males at 20 000 ppm and after 90 days in females at 20 000 ppm. A significant increase in total cytochrome P450 in males of the 3000 ppm group after 90 days was not part of a dose-related trend. With regard to thyroid-related hormones, there were consistent reductions in T_3 or T_4 that were frequently statistically significant in both sexes at 400, 3000 and 20 000 ppm at both observation times, whereas TSH concentration was significantly higher only in males of the 20 000 ppm group after 90 days.

Liver weights were increased in both sexes at 400 ppm and higher, and thyroid and adrenal weights were increased in females at 20 000 ppm (Table 13). The increases in liver and thyroid weights were accompanied by minimal to slight centrilobular hypertrophy of hepatocytes in males at 3000 ppm and higher and in females at 400 ppm and higher and minimal thyroid follicular cell hypertrophy in males at 20 000 ppm and in females at 400 ppm and higher. The liver hypertrophy without indication of hepatotoxicity was considered to be adaptive. The changes in thyroid weight, histopathology and related hormones indicated that homeostasis of the pituitary and thyroid negative feedback system was affected by the treatment in rats. Minimal to slight microvesiculation of the fascicular zone in the adrenal cortex was increased in males at 20 000 ppm at 90 days. This change was not detected in a long-term study in rats (Craig, 2011a). In a mechanistic study involving measurement of serum corticosterone levels and ultrastructural analysis of the adrenals, no functional or structural changes in the adrenal cortex were observed that were indicative of an adverse effect (see section 2.6). Therefore, the minimal to slight adrenal change was considered to be treatment related but not adverse and within normal physiological limits.

The NOAEL for the 90-day oral toxicity study in rats was 100 ppm (equal to 5.7 mg/kg bw per day), based on liver hypertrophy, decreases in thyroid hormones in both sexes and histopathological changes in the thyroid in females at 400 ppm (equal to 22 mg/kg bw per day) (Carpenter, 2007; Gannon, 2011b).

Dogs

In a 28-day feeding toxicity study, cyantraniliprole (purity 92.7%; batch no. HGW86-085) was administered to male and female Beagle dogs (two of each sex per group) at a dietary concentration of 0, 1000, 10 000 or 40 000 ppm (equal to 0, 35, 311 and 1043 mg/kg bw per day for males and 0, 35, 335 and 1240 mg/kg bw per day for females, respectively). Parameters evaluated

included body weight, body weight gain, feed consumption, feed efficiency, clinical signs, neurobehavioural

Table 12. Thyroid metabolism–related biochemical parameters in a 90-day oral toxicity study in rats

	0 ppm	100 ppm	400 ppm	3 000 ppm	20 000 ppm
Interim kill (29/30 days)					
Males					
T_4 (µg/dL)	3.7 ± 0.9	3.1 ± 0.7	2.3 ± 0.5*	2.1 ± 0.3*	2.1 ± 0.7*
T_3 (ng/dL)	70.4 ± 15.0	68.9 ± 16.4	60.6 ± 15.0	61.0 ± 23.8	55.7 ± 18.4
TSH (ng/mL)	6.8 ± 1.5	6.5 ± 1.4	6.7 ± 2.2	8.2 ± 2.9	8.3 ± 5.1
Total P450 (nmol/mg protein)	0.68 ± 0.16	0.68 ± 0.12	0.80 ± 0.20	0.81 ± 0.08	0.93 ± 0.15*
UDPGT (nmol/mg per minute)	31.2 ± 3.3	40.7 ± 7.2	45.4 ± 12.7*	45.7 ± 3.9*	55.4 ± 8.1*
Females					
T_4 (µg/dL)	3.0 ± 0.6	2.6 ± 0.8	2.1 ± 0.7*	1.4 ± 0.5*	1.3 ± 0.5*
T_3 (ng/dL)	81.3 ± 11.0	79.2 ± 11.8	62.3 ± 6.2*	68.1 ± 15.9	63.3 ± 17.4*
TSH (ng/mL)	5.9 ± 1.6	5.7 ± 0.8	5.9 ± 1.4	6.0 ± 1.2	5.9 ± 1.4
Total P450 (nmol/mg protein)	0.48 ± 0.06	0.47 ± 0.04	0.46 ± 0.08	0.50 ± 0.06	0.56 ± 0.06
UDPGT (nmol/mg per minute)	31.6 ± 2.6	40.1 ± 4.5	61.2 ± 20.0*	59.9 ± 7.7*	66.4 ± 12.2*
Terminal kill (90 days)					
Males					
T_4 (µg/dL)	4.1 ± 0.7	3.7 ± 0.5	3.1 ± 0.8*	2.8 ± 0.5*	2.9 ± 0.6**
T_3 (ng/dL)	67.4 ± 5.3	64.5 ± 9.8	55.7 ± 11.6*	53.6 ± 9.4*	52.4 ± 0.5**
TSH (ng/mL)	7.1 ± 1.0	8.2 ± 2.3	7.9 ± 2.1	10.1 ± 4.1	11.0 ± 2.0*
Total P450 (nmol/mg protein)	0.86 ± 0.09	0.95 ± 0.27	0.79 ± 0.15	1.15 ± 0.17*	1.10 ± 0.08
UDPGT (nmol/mg per minute)	51.7 ± 14.5	48.0 ± 4.5	44.9 ± 6.6	66.7 ± 8.8	75.5 ± 8.4*
Females					
T_4 (µg/dL)	2.4 ± 0.6	2.0 ± 0.7	1.4 ± 0.6	0.8 ± 0.7*	0.5 ± 0.5*
T_3 (ng/dL)	92.1 ± 7.9	91.1 ± 7.9	86.0 ± 16.3	63.3 ± 13.3*	65.0 ± 17.1*
TSH (ng/mL)	6.5 ± 0.7	6.9 ± 1.1	6.8 ± 1.0	6.7 ± 1.1	7.4 ± 1.8
Total P450 (nmol/mg protein)	0.55 ± 0.19	0.60 ± 0.10	0.67 ± 0.11	0.70 ± 0.14	0.87 ± 0.13*
UDPGT (nmol/mg per minute)	32.0 ± 5.8	38.4 ± 9.1	51.2 ± 8.0*	51.8 ± 10.7*	67.7 ± 13.1*

T_3: triiodothyronine; T_4: thyroxine; TSH: thyroid stimulating hormone; UDPGT: uridine diphosphate–glucuronosyltransferase; * $P < 0.05$
Source: Carpenter (2007)

observations, ophthalmoscopic observations, thyroid hormones, gross pathology, organ weights, histopathology, and hepatic cytochrome P450 and microsomal enzymes. This study was conducted as a non-GLP study.

Table 13. Summary of organ weights and histopathology in a 90-day oral toxicity study in rats

	0 ppm	100 ppm	400 ppm	3 000 ppm	20 000 ppm
Interim kill (29/30 days)					
Organ weights					
Males					
- Absolute liver weight (g)	13.1	12.5	13.5	14.7	15.6a
- Relative[a] liver weight (%)	3.2	3.0	3.2	3.5a	3.8a
Females					
- Absolute liver weight (g)	7.40	7.7	8.3	9.2a	9.4a
- Relative[a] liver weight (%)	3.1	3.2	3.6	4.0b	4.0b
- Absolute thyroid weight (g)	0.011	0.017	0.015	0.017	0.021
- Relative[a] thyroid weight (%)	0.005	0.007	0.006	0.008	0.009b
Histopathology					
Liver: Hypertrophy of hepatocytes, centrilobular					
- Males	0/5	0/5	0/5	0/5	0/5
- Females	0/5	0/5	0/5	3/5	5/5
Terminal kill (90 days)					
Organ weights					
Males					
- Absolute liver weight (g)	16.0	16.1	17.3	16.5	18.0a
- Relative[a] liver weight (%)	2.7	2.8	3.0a	2.9a	3.3a
- Absolute kidney weight (g)	4.3	4.2	4.5	3.9b	4.4
- Relative[a] kidney weight (%)	0.74	0.72	0.77	0.69	0.80
- Absolute thyroid weight (g)	0.032	0.028	0.033	0.034	0.034
- Relative[a] thyroid weight (%)	0.005	0.005	0.006	0.006	0.006
Females					
- Absolute liver weight (g)	8.4	8.4	9.2	10.3a	11.2a
- Relative[a] liver weight (%)	2.9	3.0	3.2	3.6a	4.1a
- Absolute kidney weight (g)	2.21	2.09	2.33	2.24	2.37
- Relative[a] kidney weight (%)	0.76	0.76	0.82	0.79	0.86a

	0 ppm	100 ppm	400 ppm	3 000 ppm	20 000 ppm
- Absolute thyroid weight (g)	0.024	0.024	0.028	0.026	0.028
- Relative[a] thyroid weight (%)	0.009	0.009	0.010	0.009	0.010
Histopathology					
Males					
- Liver: Hypertrophy of hepatocytes, centrilobular	0/10	0/10	0/10	4/10	7/10
- Thyroid: Follicular cell hypertrophy	0/10	0/10	0/10	0/10	5/10
- Adrenal: Microvesiculation in fascicular zone of cortex	0/10	0/10	0/10	1/10	6/10
Females					
- Liver: Hypertrophy of hepatocytes, centrilobular	0/10	0/10	2/10	6/10	9/10
- Thyroid: Follicular cell hypertrophy	1/10	0/10	3/10	4/10	6/10
- Adrenal: Microvesiculation in fascicular zone of cortex	0/10	0/10	0/10	2/10	2/10

a: $P < 0.05$ (Dunnett/Tamhane-Dunnett criterion); b: $P < 0.01$

[a] Relative to body weight.

Source: Carpenter (2007)

No treatment-related effects on survival, clinical or neurobehavioural findings or physical or ophthalmoscopic examinations were observed. A dose-related decreased body weight gain in both sexes at 1000 and 10 000 ppm and/or body weight losses in both sexes at 40 000 ppm, corresponding to decreases in feed consumption and feed efficiency, were observed. Effects on clinical chemistry, including increased alkaline phosphatase (AP) activity and decreased albumin levels in both sexes at 1000 ppm and higher, decreased cholesterol levels in males at 1000 ppm and higher and in females at 10 000 ppm and higher, increased gamma-glutamyltransferase (GGT) in females and increased aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) or sorbitol dehydrogenase (SDH) in both sexes at 40 000 ppm, were detected. Liver weights were increased in males at 10 000 ppm and above and in all female dose groups, but the increases were not associated with microscopic pathology except for minimal hepatocyte apoptosis observed in one female at 40 000 ppm. Induction of hepatic total cytochrome P450 and CYP2B1, CYP3A2 and CYP4A1/2/3 isozymes was observed in all male and female dose groups, but without any monotonic responses. No adverse or primary test article–related effects on thyroid hormones (TSH, total T_3, total T_4) were observed in any dose group. One male dog in the 40 000 ppm group was diagnosed with canine juvenile polyarteritis syndrome (idiopathic arteritis in dogs) because of the characteristic clinical signs and morphological features reported (Hartman, 1987; Hayes, Roberts & Halliwell, 1989; Snyder et al., 1995; Kerns, Roth & Hosokawa, 2001).

A NOAEL for the 28-day oral toxicity study in dogs was not determined, based on changes in body weight, nutritional parameters and clinical chemistry indicating hepatotoxicity in both sexes at 1000 ppm (equal to 35 mg/kg bw per day), the lowest dose tested (Luckett, 2007a).

Cyantraniliprole (purity 93.4%; batch no. HGW86-141) was administered to male and female Beagle dogs (four of each sex per group) at a dietary concentration of 0, 30, 100, 1000 or 10 000 ppm (equal to 0, 0.98, 3.08, 31.9 and 281 mg/kg bw per day for males and 0, 0.97, 3.48, 34.3 and 294 mg/kg bw per day for females, respectively) for 90 days. Parameters evaluated included mortality and morbidity, body weight, body weight gain, feed consumption, feed efficiency, compound consumption, clinical signs, neurobehavioural signs, haematology, urine analysis, clinical chemistry, ophthalmology, organ weights, and gross and microscopic pathology. Blood was collected on test day 57 (unfasted) and analysed for concentrations of parent compound and selected metabolites. The results are shown in Table 7.

One male in the 10 000 ppm diet group was dead on day 52, possibly caused by canine juvenile polyarteritis syndrome. Treatment-related reductions of body weight gain (and/or loss of body weight), feed consumption and feed efficiency were observed in both sexes at 10 000 ppm. In blood biochemistry, decreases in total protein and albumin levels in both sexes at 1000 ppm and above, a decrease in calcium levels in males at 1000 ppm and above and in females at 10 000 ppm, decreases in cholesterol and glucose levels in both sexes at 10 000 ppm and an increase in ALAT in females at 10 000 ppm were observed (Table 14). Statistically significant increases in AP were found in both sexes at 1000 ppm and above. Age-matched reduction of AP was not observed at 30 and 100 ppm in both sexes. The changes at the lower doses were considered to be treatment related, but not adverse, as there was no indication of hepatotoxicity, including histopathology, at these doses. No treatment-related effects on haematology or urine analysis were detected.

Liver weights were increased in both sexes at 1000 ppm and above. Microscopically, minimal to mild bile duct hyperplasia in all males and three females and minimal or mild focal hepatocellular necrosis in one male and three females detected at 10 000 ppm were considered to be treatment-related adverse effects. Three dogs (two males, including the dead one on day 52, and one female) at 10 000 ppm were affected by canine juvenile polyarteritis syndrome, which showed systemic distribution (e.g. heart, liver, other organs). One male affected was dead as a result of cardiac dysfunction caused by a secondary effect of this syndrome. This syndrome has been reported as idiopathic (Hartman, 1987; Hayes, Roberts & Halliwell, 1989; Snyder et al., 1995; Kerns, Roth & Hosokawa, 2001), but a possibility that the treatment exacerbated the syndrome could not be excluded, due to the occurrence of the condition only at the highest doses in both sexes and detection in both the 1-year (Luckett, 2010) and 28-day (Luckett, 2007a) oral toxicity studies of cyantraniliprole in dogs. Hepatocellular necrosis and leukocyte infiltration in sinusoids were also found in both sexes at 10 000 ppm.

The NOAEL for the 90-day oral toxicity study in dogs was 100 ppm (equal to 3.08 mg/kg bw per day), based on increased total protein, albumin concentrations and AP in males at 1000 ppm (equal to 31.9 mg/kg bw per day) (Luckett, 2007b; Gannon, 2009).

In a 1-year feeding study, cyantraniliprole (purity 94.5%; batch no. HGW86-230) was administered to groups of four Beagle dogs of each sex at a dietary concentration of 0, 40, 200, 1000 or 5000 ppm (equal to 0, 0.96, 5.67, 27.0 and 144 mg/kg bw per day for males and 0, 1.12, 6.00, 27.1 and 133 mg/kg bw per day for females, respectively) for 364 consecutive days. An additional seven dogs of each sex received cyantraniliprole at a single dietary concentration of 5000 ppm for 12 weeks. At week 12, four dogs of each sex at 5000 ppm continued to receive the treatment, whereas the remaining surviving dogs (recovery animals: two males, three females) were placed on control diet for 40 weeks to evaluate reversibility. Parameters evaluated included body weight, body weight gain, feed consumption, feed efficiency, compound consumption, clinical signs, neurobehavioural

observations, haematology, coagulation, clinical chemistry, urine analysis, ophthalmology, organ weights, and gross and

Table 14. Summary of clinical chemistry in a 90-day oral toxicity study in dogs

	0 ppm	30 ppm	100 ppm	1 000 ppm	10 000 ppm
Males					
Albumin (g/dL)					
Week 4	2.83 ± 0.49	2.95 ± 0.06	2.90 ± 0.09	2.45 ± 0.13	2.25 ± 0.06*
Week 8	2.58 ± 0.34	2.55 ± 0.10	2.50 ± 0.08	2.03 ± 0.13**	1.63 ± 0.12**
Week 12	3.00 ± 0.34	2.98 ± 0.10	2.88 ± 0.05	2.23 ± 0.10**	1.83 ± 0.31**
AP (U/L)					
Week −2	109.0 ± 30.84	91.5 ± 16.42	111.5 ± 14.43	141.3 ± 59.20	90.3 ± 20.89
Week −1	105.5 ± 21.02	103.5 ± 16.74	116.3 ± 18.32	141.5 ± 58.87	97.5 ± 20.57
Week 4	74.3 ± 12.0	83.5 ± 11.7	141.3 ± 41.3	233.0 ± 74.6**	189.3 ± 93.9*
Week 8	76.5 ± 14.4	102.0 ± 35.0	169.8 ± 78.6	276.5 ± 89.2	426.7 ± 362.3*
Week 12	65.5 ± 12.0	93.5 ± 38.9	138.3 ± 60.1	293.3 ± 115.2*	363.7 ± 246.2*
Cholesterol (mg/dL)					
Week 4	170.0 ± 37.6	185.3 ± 15.6	175.8 ± 39.7	142.5 ± 29.4	100.3 ± 14.1*
Week 8	168.3 ± 41.7	184.8 ± 15.7	161.3 ± 39.7	130.5 ± 32.2	108.0 ± 49.4
Week 12	162.8 ± 48.0	173.3 ± 18.4	154.5 ± 36.8	127.5 ± 36.4	125.3 ± 72.2
Total protein (g/dL)					
Week 4	5.48 ± 0.40	5.50 ± 0.25	5.43 ± 0.17	5.00 ± 0.22	4.83 ± 0.25*
Week 8	5.33 ± 0.15	5.25 ± 0.17	5.20 ± 0.25	4.55 ± 0.33**	4.63 ± 0.38*
Week 12	5.78 ± 0.10	5.63 ± 0.28	5.60 ± 0.26	4.83 ± 0.33**	5.07 ± 0.65
Females					
ALAT (U/L)					
Week 4	22.0 ± 4.8	27.3 ± 5.7	28.3 ± 3.4	24.0 ± 7.1	36.0 ± 2.2**
Week 8	21.3 ± 2.6	25.5 ± 3.7	26.3 ± 4.0	28.0 ± 7.5	42.5 ± 23.5
Week 12	22.8 ± 5.0	26.0 ± 6.6	27.3 ± 27.3	31.0 ± 12.8	87.5 ± 30.6**
Albumin (g/dL)					
Week 4	2.80 ± 0.29	2.85 ± 0.27	2.65 ± 0.39	2.38 ± 0.19	2.20 ± 0.08*
Week 8	2.55 ± 0.27	2.60 ± 0.14	2.40 ± 0.18	1.98 ± 0.13**	1.58 ± 0.25**
Week 12	2.95 ± 0.30	2.90 ± 0.12	2.78 ± 0.17	2.30 ± 0.00**	1.80 ± 0.20**
AP (U/L)					
Week −2	121.3 ± 24.35	108.3 ± 14.36	121.3 ± 72.02	128.8 ± 35.66	90.8 ± 14.57
Week −1	121.8 ± 29.28	98.8 ± 21.47	129.5 ± 32.42	118.3 ± 23.30	127.3 ± 15.46
Week 4	91.5 ± 12.6	113.0 ± 33.2	160.8 ± 39.7	266.3 ± 57.1*	257.3 ± 143.3*
Week 8	90.5 ± 19.5	120.316.9 ±	179.0 ± 40.4	307.0 ± 104.5	483.5 ± 321.6**
Week 12	77.3 ± 13.4	98.8 ± 21.6	142.0 ± 22.7	259.3 ± 98.7**	357.8 ± 85.9**
Cholesterol (mg/dL)					
Week 4	154.8 ± 30.6	150.3 ± 12.4	179.8 ± 27.0	156.0 ± 23.9	97.8 ± 43.6*
Week 8	155.5 ± 23.5	147.8 ± 18.9	173.3 ± 27.0	134.3 ± 15.4	114.3 ± 72.8
Week 12	161.0 ± 28.2	146.3 ± 20.6	155.3 ± 14.0	143.8 ± 17.8	90.8 ± 46.4**
Total protein (g/dL)					
Week 4	5.08 ± 0.30	5.33 ± 0.13	5.38 ± 0.25	5.13 ± 0.30	4.63 ± 0.05*
Week 8	4.98 ± 0.24	5.08 ± 0.05	5.33 ± 0.42	4.60 ± 0.25	4.45 ± 0.38
Week 12	5.33 ± 0.26	5.43 ± 0.13	5.58 ± 0.38	4.93 ± 0.32	4.50 ± 0.12**

ALAT: alanine aminotransferase; AP: alkaline phosphatase; U: units; *: $P < 0.05$; **: $P < 0.01$

[a] $n = 3$ for 10 000 ppm males at weeks 8 and 12.

Source: Luckett (2007b)

microscopic pathology. Concentrations of test article and selected environmental metabolites in plasma were evaluated at week 39. The results are shown in Table 7.

One male and one female at 5000 ppm were euthanized in extremis on days 80 and 176, respectively. Their causes of death were possibly associated with juvenile canine polyarteritis, which especially affected the coronary artery or artery adjacent to the aorta in the male and the artery adjacent to the brachiocephalic trunk in the female, respectively. Mean body weight gains in both sexes at 5000 ppm and in females at 1000 ppm were decreased (Table 15).

Table 15. Mean body weight gain in the 1-year oral toxicity study in dogs

	Mean body weight gain (kg)					
	Main study					Recovery[a]
	0 ppm	40 ppm	200 ppm	1 000 ppm	5 000 ppm	5 000 ppm
Males						
Weeks −1 to 12	1.2 ± 0.5	1.6 ± 0.3	1.4 ± 0.5	1.1 ± 0.3	0.9 ± 0.4	1.2 ± 0.1
Weeks −1 to 52	1.7 ± 0.4	2.1 ± 1.4	2.1 ± 0.7	1.6 ± 0.9	1.1 ± 1.1	1.7 ± 0.6
Females						
Weeks −1 to 12	0.7 ± 0.5	1.3 ± 0.8	0.6 ± 0.4	0.7 ± 0.3	0.5 ± 0.4	1.2 ± 0.5
Weeks −1 to 52	1.5 ± 0.4	2.1 ± 1.4	1.3 ± 0.3	0.9 ± 0.5	0.1 ± 0.7	2.0 ± 1.2

[a] Two males and three females at 5000 ppm were placed on recovery following 12 weeks (84 days) of administration.

Source: Luckett (2010)

Adverse test article–related increases in ALAT at 1000 ppm and higher and in GGT at 5000 ppm and decreases in total protein and albumin levels at 1000 ppm and higher were observed in males and females (Table 16). Consistently decreased levels of cholesterol observed in both sexes at 1000 ppm and above were also considered treatment related. The decrease in females at 200 ppm at termination was not considered toxicologically significant due to the consistently lower values before the treatment in this group (Table 16).

Clear increases in AP observed in both sexes at 1000 ppm and above were considered to be adverse due to other changes suggesting liver toxicity at those doses, described below. AP was slightly increased in both sexes at 200 ppm. In addition, increased liver weights were observed in males, suggesting that the marginal increase in AP was adverse. The age-matched decrease in AP was not observed in males at 40 ppm, but no histopathological or functional change in the liver was found at 40 ppm. In addition, individual values of AP in the male control group before treatment were lower compared with other treated groups and the control group in the 90-day dog study (Luckett, 2007b). Thus, the increase in males at 40 ppm was not considered to be adverse.

Liver (with gallbladder) weights (absolute and/or relative to body weight and to brain weight) at 200 ppm and above in both sexes and thyroid weight (absolute and relative) at 5000 ppm in males were increased. Microscopically, the increased liver weights were associated with degenerative changes in hepatocytes, with enlargement, rarefaction and margination of cytoplasm, vacuolation, cytoplasmic membrane inclusion and/or single-cell necrosis in the centrilobular area and chronic inflammatory change in the portal area at 1000 ppm and above in both sexes (Table 17). In addition, minimal cholestasis was detected in males at 1000 ppm and above and in females at 5000 ppm. Mucosal hyperplasia in the gallbladder was observed at 5000 ppm in both sexes. These effects were reversible, as there was no clinical pathology or microscopic findings at termination in the 5000 ppm recovery group. Arteritis and/or perivasculitis in individual organs (e.g. coronary artery, heart, liver, kidney or brain) were observed in control and treated groups in both sexes. Systemic arteritis was observed in two males and one female at 5000 ppm. These arterial changes were similar to those observed at 10 000 ppm in an earlier 90-day study with cyantraniliprole (Luckett, 2007b). The

morphological characteristics of arteritis and/or perivasculitis were identical to those of canine juvenile polyarteritis (Hartman, 1987; Hayes, Roberts & Halliwell, 1989; Snyder et al., 1995). Whereas the arteritis has been reported to be idiopathic (Hartman, 1987; Hayes, Roberts & Halliwell, 1989; Snyder et al., 1995), a possibility of acceleration by the treatment could not be excluded due to the consistency of the observations with the previous 90-day (Luckett, 2007b) and 28-day (Luckett, 2007a) dog studies at the high dose in both sexes.

Table 16. Selected clinical chemistry parameters in the 1-year oral toxicity study in dogs

	Week	Main study					Recovery[a]
		0 ppm	40 ppm	200 ppm	1 000 ppm	5 000 ppm	5 000 ppm
Males							
AP (U/L)	−3	41.0 ± 9.38	61.5 ± 15.36	57.8 ± 11.58	52.0 ± 9.38	58.2 ± 20.86	54.5 ± 27.58
	−2	37.8 ± 9.60	65.5 ± 14.62	48.5 ± 10.28	46.8 ± 9.84	53.6 ± 19.60	58.0 ± 33.94
	13	26.8 ± 6.8	70.0 ± 9.9**	109.8 ± 10.2**	174.3 ± 51.0**	318.8 ± 159.7**	354.5 ± 24.8
	26	23.5 ± 8.7	79.0 ± 15.1**	125.0 ± 25.2**	207.8 ± 76.1	402.8 ± 198.8	37.0 ± 17.0
	52	17.3 ± 4.6	71.5 ± 17.2**	117.5 ± 9.6**	209.5 ± 105.7	401.0 ± 171.9	28.5 ± 13.4
GGT (U/L)	13	3.0 ± 0.0	3.3 ± 0.5	4.0 ± 0.8	3.8 ± 1.0	5.0 ± 2.2	4.0 ± 1.4
	26	2.5 ± 0.6	3.0 ± 0.8	3.8 ± 1.0	4.0 ± 1.4	4.5 ± 1.3	2.5 ± 0.7
	52	4.5 ± 0.6	4.3 ± 1.0	4.5 ± 1.9	5.8 ± 1.5	8.0 ± 2.2	5.0 ± 0.0
ALAT (U/L)	13	32.3 ± 12.7	31.0 ± 2.9	42.0 ± 18.0	43.0 ± 8.9	67.0 ± 32.7	46.5 ± 9.2
	26	31.5 ± 11.6	33.5 ± 7.5	53.3 ± 13.5	50.8 ± 16.9	94.0 ± 40.2	31.0 ± 0.0
	52	33.0 ± 11.3	36.0 ± 5.7	59.5 ± 27.5	95.8 ± 50.5	112.5 ± 39.2	32.0 ± 0.0
Total protein (g/dL)	13	6.3 ± 0.4	6.0 ± 0.3	5.8 ± 0.2	5.4 ± 0.2*	5.6 ± 0.4	5.4 ± 0.0
	26	6.1 ± 0.5	5.9 ± 0.1	5.5 ± 0.2	5.2 ± 0.1	5.4 ± 0.6	6.0 ± 0.4
	52	6.3 ± 0.5	5.9 ± 0.1	5.6 ± 0.1	5.3 ± 0.2	5.7 ± 0.4	6.1 ± 0.4
Albumin (g/dL)	13	3.2 ± 0.2	2.8 ± 0.2	2.6 ± 0.2*	2.4 ± 0.2**	2.3 ± 0.2**	2.2 ± 0.1
	26	3.2 ± 0.2	2.8 ± 0.2	2.6 ± 0.2*	2.4 ± 0.2**	2.2 ± 0.3**	3.2 ± 0.4
	52	3.2 ± 0.1	2.9 ± 0.1*	2.6 ± 0.2*	2.4 ± 0.1**	2.2 ± 0.4**	3.1 ± 0.4
Cholesterol (mg/dL)	13	155.3 ± 23.8	187.8 ± 27.0	162.8 ± 42.0	102.8 ± 15.5	90. 5 ± 21.63*	128.0 ± 18.4
	26	144.5 ± 17.3	182.5 ± 34.5	148.5 ± 39.7	99.5 ± 13.6*	97.5 ± 32.4	158.5 ± 38.9
	52	145.5 ± 23.2	185.0 ± 24.4	134.3 ± 21.5	95.8 ± 24.1	108.0 ± 30.8	165.0 ± 48.1
Females							
AP (U/L)	−3	74.5 ± 22.83	46.8 ± 1.71	55.8 ± 15.00	60.8 ± 3.95	68.3 ± 14.66	56.3 ± 5.03
	−2	71.3 ± 15.24	41.8 ± 4.19	58.3 ± 17.33	57.8 ± 2.22	70.5 ± 16.13	52.0 ± 8.89
	13	43.8 ± 13.5	54.3 ± 14.9	142.0 ± 76.0	229.8 ± 115.2*	369.0 ± 134.2**	261.7 ± 79.3*
	26	53.5 ± 42.4	65.3 ± 27.4	151.8 ± 69.8	237.3 ± 77.5	445.0 ± 325.6**	43.3 ± 14.0
	52	38.8 ± 14.7	58.0 ± 20.8	151.0 ± 55.4	280.0 ± 77.3*	591.3 ± 254.7**	39.0 ± 4.6
GGT (U/L)	13	3.5 ± 0.6	4.3 ± 2.1	3.8 ± 0.5	4.5 ± 1.3	6.0 ± 0.0*	4.7 ± 1.5
	26	3.3 ± 0.5	3.0 ± 1.2	3.0 ± 0.0	5.0 ± 2.2	7.0 ± 1.0**	2.3 ± 0.6
	52	5.3 ± 1.0	5.0 ± 1.2	5.5 ± 0.6	7.3 ± 2.6	10.3 ± 1.2**	4.3 ± 1.5

Table 16 (continued)

	Week	Main study					Recovery[a]
		0 ppm	40 ppm	200 ppm	1 000 ppm	5 000 ppm	5 000 ppm
ALAT (U/L)	13	26.8 ± 3.0	25.3 ± 3.2	28.8 ± 7.9	41.5 ± 18.1	66.8 ± 29.9*	44.0 ± 18.3
	26	21.0 ± 3.8	26.3 ± 3.6	26.0 ± 6.6	58.8 ± 41.3	117.0 ± 58.4**	21.3 ± 3.1
	52	22.3 ± 3.4	25.5 ± 3.1	26.5 ± 7.1	83.5 ± 74.5	109.0 ± 50.1*	20.7 ± 1.2
Total protein (g/dL)	13	6.0 ± 0.2	6.0 ± 0.4	5.8 ± 0.4	5.2 ± 0.2**	5.2 ± 0.2**	5.1 ± 0.2
	26	5.8 ± 0.3	5.90.4 ±	5.6 ± 0.4	5.0 ± 0.3**	4.9 ± 0.1**	5.8 ± 0.1
	52	6.0 ± 0.2	6.2 ± 0.3	5.6 ± 0.4	5.2 ± 0.2**	4.9 ± 0.2**	6.1 ± 0.3
Albumin (g/dL)	13	3.1 ± 0.2	3.0 ± 0.1	2.9 ± 0.2	2.4 ± 0.1**	2.4 ± 0.2**	2.2 ± 0.3**
	26	3.1 ± 0.3	3.1 ± 0.3	2.9 ± 0.3	2.4 ± 0.2**	2.2 ± 0.0**	2.9 ± 0.3
	52	3.2 ± 0.2	3.1 ± 0.2	2.9 ± 0.2	2.4 ± 0.2**	2.1 ± 0.1**	2.9 ± 0.2
Cholesterol (mg/dL)	–3	173.3 ± 43.1	148.8 ± 14.5	130.8 ± 15.7	156.0 ± 31.9	142.3 ± 8.18	136.3 ± 21.7
	–2	172.0 ± 34.0	144.0 ± 11.34	151.5 ± 23.1	156.0 ± 31.89	161.0 ± 11.46	140.7 ± 24.4
	13	169.8 ± 43.3	158.0 ± 16.0	152.8 ± 12.7	131.5 ± 31.7	115.5 ± 39.8	99.3 ± 2.1*
	26	200.5 ± 31.4	151.8 ± 15.4	149.5 ± 17.9	118.5 ± 32.7**	132.0 ± 12.5	215.0 ± 64.2
	52	249.8 ± 109.2	163.0 ± 13.1	138.5 ± 10.9*	122.3 ± 38.1*	121.7 ± 30.2*	265.7 ± 60.1

ALAT: alanine aminotransferase; AP: alkaline phosphatase; GGT: gamma-glutamyltransferase; U: units; *: $P < 0.05$; **: $P < 0.01$

[a] Recovery group (individuals dosed through week 12); statistics were not run on males of the recovery group because there were two males only.

Source: Luckett (2010)

Table 17. Summary of liver histopathology in a 1-year oral toxicity study in dogs

	Males						Females					
	0 ppm	40 ppm	200 ppm	1 000 ppm	5 000 ppm	Recovery	0 ppm	40 ppm	200 ppm	1 000 ppm	5 000 ppm	Recovery
No. of dogs examined	4	4	4	4	5[a]	2	4	4	4	4	5[a]	2
Canine juvenile polyarteritis												
Systemic	0	0	0	0	2[a]	0	0	0	0	0	1[a]	0
Single organ	1	0	0	3	1	0	1	1	1	0	0	0
Liver												
Cholestasis	0	0	0	1	3	0	0	0	0	0	1	0
Degeneration, hepatocellular	0	0	0	2	4	0	0	0	0	4	3	0
Inflammation, chronic active	0	0	0	0	4[a]	0	0	0	0	2	3	0
Gallbladder												
Hyperplasia, mucosal	0	0	0	0	3	0	0	0	0	0	1	0

[a] Including one male (No. 136) and one female (No. 140) euthanized due to canine juvenile polyarteritis at days 80 and 176, respectively.

Source: Luckett (2010)

The NOAEL in the 1-year oral toxicity study in dogs was 40 ppm (equal to 0.96 mg/kg bw per day), based on marginal increases in AP levels without histopathological change in the liver in both sexes, increased liver weights in males and decreased cholesterol in females at 200 ppm (equal to 5.67 mg/kg bw per day) (Luckett, 2010).

(b) Dermal application

Rats

In a 28-day dermal study, cyantraniliprole (purity 94.5%; batch no. HGW86-230) was applied to the shaved, intact dorsal skin of male and female Hsd:Sprague-Dawley® rats (10 of each sex per group). The test substance was moistened with distilled water and applied for 29 daily (consecutive) applications. The rats were exposed to the test substance for 6 hours/day. Exposure doses were 0, 100, 300 and 1000 mg/kg bw per day. Parameters evaluated included body weight, body weight gain, feed consumption, feed efficiency, clinical signs, dermal irritation, clinical pathology, ophthalmology, organ weights, and gross and microscopic pathology.

There were no effects on mortality, body weights, nutritional parameters, ophthalmology, organ weights, or clinical or anatomic pathology parameters. Slight or mild erythema was observed at the dose site of male and female rats in all treated groups; the occurrence was less frequent in females than in males. One male at 100 mg/kg bw per day exhibited oedema, and one female in the control group exhibited slight erythema but no oedema at the dose site. Although the dermal irritation was considered to be test substance related, it was not considered adverse.

The NOAEL for dermal toxicity in rats was 1000 mg/kg bw per day, the highest dose tested (Lowe, 2009).

2.3 Long-term studies of toxicity and carcinogenicity

Mice

In an 18-month carcinogenicity feeding study, cyantraniliprole (purity 97%; batch no. HGW86-412) was administered to male and female Crl:CD1®(ICR) mice (60 of each sex per group) at a dietary concentration of 0, 20, 150, 1000 or 7000 ppm (equal to 0, 2.0, 15.5, 104 and 769 mg/kg bw per day for males and 0, 2.4, 18.6, 131 and 904 mg/kg bw per day for females, respectively). Parameters evaluated included body weight, body weight gain, feed consumption, feed efficiency, clinical signs, clinical pathology, ophthalmology, organ weights, gross pathology and histopathology.

No treatment-related effects were observed on survival, nutritional parameters, clinical or ophthalmological signs of toxicity or clinical pathology parameters. Body weight gain was depressed in males at 7000 ppm. Thyroid weight (relative to body weight) was increased in males at 7000 ppm, although corresponding morphological findings were not observed. Increases in liver weight in both sexes at 1000 ppm and above were correlated with an increased incidence of hepatocellular hypertrophy at the same concentrations. Hepatocellular hypertrophy in the absence of hepatotoxicity was not considered to be adverse. There were no increases in tumour incidence or in any treatment-related non-neoplastic microscopic pathology.

The NOAEL for toxicity in mice was 1000 ppm (equal to 104 mg/kg bw per day), based on a decrease in body weight gain and increased thyroid weight in males at 7000 ppm (equal to 769 mg/kg bw per day). The NOAEL for carcinogenicity in mice was 7000 ppm (equal to 769 mg/kg bw per day), the highest dose tested (Craig, 2011b).

Rats

In a 2-year chronic toxicity and carcinogenicity feeding study, cyantraniliprole (purity 97%; lot no. 9182-7; batch no. HGW86-412) was administered to male and female Crl:CD®(SD) rats (70 of each sex per group) at a dietary concentration of 0, 20, 200, 2000 or 20 000 ppm (equal to 0, 0.8, 8.3, 84.8 and 907 mg/kg bw per day for males and 0, 1.1, 10.5, 107 and 1161 mg/kg bw per day for females, respectively). Ten rats per group were examined after approximately 1 year on study, and all surviving rats were euthanized after approximately 2 years on study. Parameters evaluated included

body weight, body weight gain, feed consumption, feed efficiency, clinical signs, clinical pathology, ophthalmology, organ weights, and gross and microscopic pathology.

There were no treatment-related effects on survival or on clinical or ophthalmological observations, and there was no increase in the incidence of observed masses. At 20 000 ppm, there were small reductions in body weight, body weight gain and feed efficiency in both sexes, primarily over the first 1–1.5 years. In addition, there was a slight decrease in body weight gain (90% compared with the control value) in females at 2000 ppm during the first 3 months. Three male rats at 20 000 ppm had increases in liver enzyme levels at 12 months. In blood biochemistry at interim kill, increases in GGT, ASAT, ALAT and SDH compared with control values were detected in males at 20 000 ppm. Liver weights were increased at 2000 ppm (12 months) and 20 000 ppm (12 and 24 months) in males and at 2000 ppm and above (12 months only) in females. Test substance–related histopathological changes were observed in liver of males after 12 months and in liver and kidney of females (Table 18). Hepatocellular hypertrophy in the centrilobular area was observed in both sexes at 2000 ppm and above at 12 and 24 months. Increases in focus of cellular alterations (eosinophilic, basophilic or clear) were noted in males at 2000 ppm (clear only) and 20 000 ppm. Incidence of focal vacuolation of hepatocytes was increased in males at 2000 ppm and higher. In females, the incidence of chronic progressive nephropathy was slightly increased at 20 000 ppm; however, the relationship of this finding with the treatment was not clear due to the common occurrence of this disease in aged rats. Erosion/ulcer or epithelial hyperplasia in the non-glandular stomach was slightly increased in females at 20 000 ppm; however, the relationship of these findings with treatment was not determined. No increased incidences of tumours were detected in any treated groups.

Table 18. Summary of non-neoplastic histopathology in a combined oral toxicity and carcinogenicity study in rats

	0 ppm	20 ppm	200 ppm	2 000 ppm	20 000 ppm
Males					
12 months					
Liver: Hepatocyte hypertrophy, centrilobular	0/10	0/10	0/10	5/10*	8/10*
24 months					
Liver					
- Hepatocyte hypertrophy, centrilobular	0/60	0/60	0/60	0/60	6/60#*
- Focus of cellular alteration, clear	0/60	0/60	1/60	4/60#	5/60#
- Focus of cellular alteration, eosinophilic	20/60	15/60	12/60	29/60	32/60#*
- Focus of cellular alteration, basophilic	10/60	9/60	9/60	12/60	20/60#
- Vacuolation of hepatocyte, focal	4/60	4/60	7/60	13/60#*	13/60#*
Females					
12 months					
Liver					
- Hepatocyte hypertrophy, centrilobular	0/10	0/10	0/10	4/10	6/10*
- Hepatocyte hypertrophy, panlobular	0/10	0/10	0/10	0/10	1/10
24 months					
Liver					
- Hepatocyte hypertrophy, centrilobular	0/60	0/60	0/60	9/60#*	22/60#*
Kidney					
- Nephropathy, chronic progressive	34/60	37/60	32/60	44/60	45/60#
Stomach, non-glandular					
- Erosion/ulcer	0/60	1/60	0/60	0/60	5/60
- Epithelial hyperplasia	1/60	2/60	2/60	3/60	6/60

#: $P < 0.05$ (Cochran-Armitage trend test); *: $P < 0.05$ (Fisher's exact test)
Source: Craig (2011a)

The NOAEL in the 2-year oral toxicity study in rats was 200 ppm (equal to 8.3 mg/kg bw per day), based on increased incidences of foci of cellular alteration in the liver in males and hepatocellular vacuolation in both sexes and slight depression of body weights in females at 2000 ppm (equal to 84.8 mg/kg bw per day). The NOAEL for carcinogenicity in rats was 20 000 ppm (equal to 907 mg/kg bw per day), the highest dose tested (Craig, 2011a).

2.4 Genotoxicity

Cyantraniliprole was tested for genetic toxicity and mutagenic potential in a battery of in vitro and in vivo studies (Table 19). These were in vitro tests for gene mutation induction in *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A and mammalian cells (Chinese hamster ovary fibroblasts), for clastogenicity in cultures of human lymphocytes and for micronucleus induction in bone marrow cells of mice treated in vivo orally by gavage on a single occasion and sampled 24 and 48 hours later. No activity was observed in any of these assays that was considered indicative of adverse effects on genetic material. A statistically significant increase in micronuclei observed at 2000 mg/kg bw in male mice at the 48-hour sampling time (3/2000 cells compared with 0/2000 cells in the controls) was considered spurious by the authors, because it was within the laboratory's historical control range.

Table 19. Summary of genotoxicity studies with cyantraniliprole

Type of study	Batch no.	Test system	Concentration range tested	Result	Reference
In vitro bacterial mutagenicity (Ames)	HGW86-412	*Salmonella typhimurium* and *Escherichia coli*	1.5–5 000 µg/plate (±S9)	Negative	Wagner & VanDyke (2009a)
In vitro chromosomal aberration (clastogenicity)	HGW86-412	Human lymphocytes	125–3 500 µg/mL (4 h, ±S9) 15.7–1 500 µg/mL (20 h, −S9)	Negative	Gudi & Rao (2009)
In vitro mammalian cell mutagenicity (CHO/HPRT)	HGW86-412	CHO cells	10–1 000 µg/mL (±S9)	Negative	Stankowski (2011)
In vivo micronucleus	HGW86-412	Mouse bone marrow	Male and female: 500–2 000 mg/kg bw	Negative	Donner (2011)
In vivo micronucleus	HGW86-014	Rat peripheral blood	Male and female: 2 000 mg/kg bw	Negative	Nabb (2010)

CHO: Chinese hamster ovary; HPRT: hypoxanthine–guanine phosphoribosyltransferase; S9: 9000 × *g* supernatant fraction of rat liver homogenate

2.5 Reproductive and developmental toxicity

(a) Multigeneration reproduction study

Rats

In a two-generation reproduction study, cyantraniliprole (purity 94.5%; batch no. HGW86-230) was administered to male and female Crl:CD®(SD) rats (150 of each sex per group for both the P and F_1 generations) at a dietary concentration of 0, 20, 200, 2000 or 20 000 ppm. The P rats were bred within their treatment groups to produce F_1 litters after 70 days on test. The F_1 rats were bred within their respective treatment groups to produce F_2 litters at least 86 days after weaning.

Parameters evaluated included body weight, body weight gain, feed consumption, feed efficiency, clinical signs, reproductive indices, litter and pup parameters, estrous cycle, sperm parameters, organ weights, and gross and microscopic pathology.

The achieved doses for each parental generation are shown in Table 20.

Table 20. The achieved doses for each parental generation in a reproductive toxicity study in rats

Generation	Feeding period (days)	Achieved doses (mg/kg bw per day)			
		20 ppm	200 ppm	2 000 ppm	20 000 ppm
P males	Premating 1–70	1.1	11.0	110	1 125
P females	Premating 1–70	1.4	13.9	136	1 344
	Gestation 0–21	1.4	13.3	135	1 353
	Lactation 1–15	2.7	27.0	283	2 782
F_1 males	Premating 1–70	1.4	14.6	151	1 583
F_1 females	Premating 1–70	1.9	20.1	203	2 125
	Gestation 0–21	1.4	14.7	149	1 518
	Lactation 1–15	2.7	27.4	277	2 769

Source: Barnett (2011)

In the P and F_1 parental generations, no treatment-related clinical signs were detected. Slight reductions in body weight gain and nutritional parameters in parental animals at 20 000 ppm in both sexes were detected throughout the study, including premating, gestation and lactation periods. There was no adverse treatment-related reproductive toxicity at any level tested in this study up to and including 20 000 ppm. Increases in liver weight accompanied by hepatocellular hypertrophy were observed at 2000 and 20 000 ppm in both sexes of the P and F_1 generations (Table 21). Thyroid weights were marginally increased at 2000 and 20 000 ppm in males and at 200, 2000 and 20 000 ppm in females in the P and F_1 generations. Follicular cell hypertrophy was observed in the thyroid in the P and F_1 generations of both sexes at 2000 and 20 000 ppm. The liver hypertrophy with the change in thyroid metabolism at 2000 ppm and above was considered adverse. The minimal increases in thyroid weight with no accompanying morphological changes or liver effects in P and F_1 females at 200 ppm were not toxicologically significant (Table 22).

Thymus weights were decreased in P females at 2000 and 20 000 ppm and in F_1 females at 20 000 ppm (Table 21). Microscopically, atrophy of thymus was observed in P females at these doses (1/29, 2/29, 2/30, 6/29 and 10/29 at 0, 20, 200, 2000 and 20 000 ppm, respectively), but not in F_1 females. Vacuoles in the fascicular zone cells of the adrenal cortex accompanied by slightly increased adrenal weights were similar to changes observed in the 90-day oral toxicity studies in mice and rats (see section 2.2). The vacuolation was not considered to be adverse because there was no functional or ultrastructural damage to the adrenal cortex (see section 2.6). Therefore, the minimal to slight adrenal change was considered to be treatment related but not adverse and within normal physiological limits.

Data on reproductive toxicity, including estrous cyclicity and sperm analyses, mating behaviour, conception and fertility, parturition, gestation length, lactation, weaning and the development of offspring, except onset of puberty, were similar across all groups tested. In F_1 female rats, the average date on which vaginal opening occurred was delayed (2.2 days) at 20 000 ppm compared with the control rats. The mean value of 35.1 days at 20 000 ppm was within the testing laboratory's historical control range (mean 32.7 days; range 30.1–35.3 days). Further, the delay was not statistically significant when adjusted for body weight. The delay in time to vaginal opening was considered to be due to overall lower body weight in the F_1 generation females at weaning and persistence of the lower body weight after weaning. Therefore, the delay of puberty in F_1 females at

20 000 ppm was considered to be a secondary effect of reduced body weight at this dose. In addition, an increase in the number of F_1 pups observed with mild dehydration was noted at 20 000 ppm.

Table 21. Summary of organ weights in the P and F_1 parental generations in a reproductive toxicity study in rats

	0 ppm	20 ppm	200 ppm	2 000 ppm	20 000 ppm
Liver weight					
P males					
Absolute weight (g)	23.5	23.9	23.4	25.2	26.1*
Relative weight[a] (%)	3.6	3.6	3.6	4.0*	4.2*
P females					
Absolute weight (g)	15.8	15.5	15.6	18.8*	21.3*
Relative weight[a] (%)	4.5	4.5	4.6	5.5*	6.2*
F_1 males					
Absolute weight (g)	23.8	25.2	24.4	25. 5	25.3
Relative weight[a] (%)	3.9	3.9	3.9	4.2*	4.6*
F_1 females					
Absolute weight (g)	16.0	15.9	16.6	19.1**	21.2**
Relative weight[a] (%)	4.5	4.4	4.7	5.5**	6.2**
Thyroid/parathyroid weight					
P males					
Absolute weight (g)	0.05	0.05	0.04	0.05	0.06*
Relative weight[a] (% × 1000)	7.424	6.980	6.653*	7.588	8.892*
P females					
Absolute weight (g)	0.04	0.04	0.05*	0.05*	0.05*
Relative weight[a] (% × 1000)	10.97	10.85	13.61*	15.01*	13.80*
F_1 males					
Absolute weight (g)	0.04	0.05	0.05	0.05	0.05*
Relative weight[a] (% × 1000)	7.088	7.139	7.509	7.563	8.827*
F_1 females					
Absolute weight (g)	0.03	0.03	0.04*	0.04*	0.04*
Relative weight[a] (% × 1000)	9.3	9.0	10.4*	10.5*	11.5*
Adrenal (left adrenal)					
F_1 females					
Absolute weight (g)	0.04	0.04	0.05*	0.05*	0.05*
Relative weight[a] (% × 1000)	11.3	11.9	13.1*	14.4*	14.4*
Thymus					
P females					
Absolute weight (g)	0.18	0.17	0.18	0.14*	0.13*
Relative weight[a] (%)	0.05	0.05	0.05	0.04	0.04
F_1 females					
Absolute weight (g)	0.26	0.27	0.28	0.22	0.17*
Relative weight[a] (%)	0.07	0.08	0.08	0.06	0.06

*: $P < 0.05$; **: $P < 0.01$

[a] Relative to body weight.

Source: Barnett (2011)

Table 22. Selected histopathological changes in P and F_1 generations in a reproductive toxicity study in rats

	Males					Females				
	0 ppm	20 ppm	200 ppm	2 000 ppm	20 000 ppm	0 ppm	20 ppm	200 ppm	2 000 ppm	20 000 ppm
P parent										
Liver: Centrilobular hypertrophy of hepatocyte	0/25	0/30	0/29	28/30	29/29	1/29	0/29	0/30	27/29	30/30
Thyroid: Follicular cell hypertrophy	4/30	2/30	3/29	19/30	28/30	3/29	5/29	5/29	16/29	25/30
F_1 parent										
Liver: Centrilobular hypertrophy of hepatocyte	0/30	0/30	0/29	29/30	30/30	1/30	0/29	0/29	23/30	28/30
Thyroid: Follicular cell hypertrophy	1/30	2/30	7/29	18/30	27/30	1/30	1/29	5/29	16/30	24/30

Source: Barnett (2011)

In pups, lower body weights observed at 20 000 ppm in the F_1 generation on postnatal days (PNDs) 15 and 22 (14% lower at PND 22) and in the F_2 generation during lactation (15% lower at PND 22) were considered to be treatment related (Table 23). In the 200 and 2000 ppm groups, lower body weights detected in F_2 generation pups during the lactation period were minimal (6% and 7% lower at PND 22, respectively) (Table 23). Therefore, the lower body weights at 200 and 2000 ppm were not considered to be adverse. Weights of thymus, spleen or adrenal were decreased at 2000 or 20 000 ppm, but the decreases were not accompanied by histopathological changes (Table 24). The decreases at those doses were considered to correspond to the lower body weights at those doses and not to a direct effect on the thymus and spleen. Therefore, the lower weights of thymus and spleen were not considered to be adverse. Lower brain weights at 200 ppm and above in the F_2 generation were very minimal (within 6%), and therefore the reduced weights were not considered to be toxicologically significant.

Table 23. Body weight changes in F_1 and F_2 pups in the reproductive toxicity study in rats

	0 ppm	20 ppm	200 ppm	2 000 ppm	20 000 ppm
F_1 generation					
At birth	7.0 ± 0.6	7.1 ± 1.2	6.8 ± 0.6	6.7 ± 0.7	7.0 ± 0.8
Day 5 post-culling	10.7 ± 1.6	12.0 ± 2.7	10.8 ± 1.1	10.3 ± 1.3	10.9 ± 1.3
Day 8	16.7 ± 2.9	18.5 ± 3.8	16.8 ± 1.6	16.7 ± 2.6	16.6 ± 2.2
Day 15	34.7 ± 5.4	35.7 ± 5.0	32.8 ± 4.6	33.7 ± 4.7	31.0 ± 6.2*
Day 22	56.7 ± 7.9	57.5 ± 6.4	53.4 ± 6.5	53.6 ± 6.6	49.0 ± 7.8**
F_2 generation					
At birth	6.8 ± 0	6.5 ± 0.6	6.3 ± 0.7*	6.3 ± 0.7*	6.1 ± 0.5*
Day 5 post-culling	11.0 ± 1.6	10.7 ± 1.4	10.3 ± 1.4	9.9 ± 1.4*	9.6 ± 1.0*
Day 8	18.2 ± 2.0	17.8 ± 2.3	16.7 ± 1.7*	16.7 ± 2.0*	15.5 ± 1.6*
Day 15	37.5 ± 2.9	37.1 ± 3.4	35.0 ± 2.4*	34.7 ± 3.0*	32.4 ± 2.5*
Day 22	59.7 ± 4.9	57.6 ± 5.2	55.9 ± 4.3*	55.4 ± 4.5*	50.7 ± 4.4*

*: $P < 0.05$
Source: Barnett (2011)

Table 24. Summary of organ weights of F_1 and F_2 pups in the reproductive toxicity study in rats

	F_1 and F_2 pup organ weights (g/litter)				
	0 ppm	20 ppm	200 ppm	2 000 ppm	20 000 ppm
Thymus					
F_1 males	0.27 ± 0.06	0.28 ± 0.05	0.25 ± 0.07	0.24 ± 0.05	0.21 ± 0.06*
F_1 females	0.27 ± 0.05	0.28 ± 0.04	0.24 ± 0.04	0.24 ± 0.06	0.21 ± 0.06*
F_2 males	0.26 ± 0.05	0.25 ± 0.05	0.25 ± 0.04	0.22 ± 0.05*	0.21 ± 0.03*
F_2 females	0.27 ± 0.05	0.26 ± 0.05	0.26 ± 0.04	0.23 ± 0.05*	0.20 ± 0.03*
Spleen					
F_1 males	0.29 ± 0.07	0.30 ± 0.05	0.27 ± 0.06	0.25 ± 0.06	0.26 ± 0.18
F_1 females	0.30 ± 0.07	0.30 ± 0.07	0.27 ± 0.05	0.26 ± 0.06	0.22 ± 0.07*
F_2 males	0.30 ± 0.07	0.27 ± 0.06*	0.28 ± 0.06	0.26 ± 0.05*	0.21 ± 0.04*
F_2 females	0.30 ± 0.06	0.26 ± 0.06*	0.28 ± 0.04	0.26 ± 0.05*	0.22 ± 0.04*
Brain					
F_1 males	1.60 ± 0.10	1.63 ± 0.09	1.59 ± 0.11	1.61 ± 0.11	1.55 ± 0.14
F_1 females	1.54 ± 0.11	1.60 ± 0.09	1.54 ± 0.09	1.55 ± 0.08	1.47 ± 0.14*
F_2 males	1.64 ± 0.08	1.62 ± 0.07	1.60 ± 0.09*	1.59 ± 0.07*	1.54 ± 0.06*
F_2 females	1.60 ± 0.07	1.58 ± 0.07	1.56 ± 0.06*	1.55 ± 0.07*	1.51 ± 0.07*
Adrenal					
F_2 males	0.019 ± 0.005	0.019 ± 0.004	0.018 ± 0.003	0.019 ± 0.004	0.017 ± 0.003
F_2 females	0.020 ± 0.005	0.018 ± 0.003	0.018 ± 0.002	0.017 ± 0.004	0.016 ± 0.004*

*: $P < 0.05$
Source: Barnett (2011)

In the multigeneration reproduction study in rats, the NOAEL for parental toxicity was 200 ppm (equal to 11.0 mg/kg bw per day), based on hepatocellular hypertrophy and thyroid follicular cell hypertrophy in both sexes at 2000 ppm (equal to 110 mg/kg bw per day) in the P generation. The NOAEL for reproductive toxicity was 20 000 ppm (equal to 1344 mg/kg bw per day), based on no effects on reproductive indicators at the highest dose tested. The NOAEL for offspring toxicity was 2000 ppm (equal to 280 mg/kg bw per day, the mean dose for P and F_1 parental females during lactation), based on lower body weights of F_1 and F_2 generation pups at 20 000 ppm (equal to 2776 mg/kg bw per day, the mean dose for P and F_1 parental females during lactation) (Barnett, 2011).

(b) Developmental toxicity

Rats

In a developmental toxicity study, cyantraniliprole (purity 94.5%; batch no. HGW86-230) was administered by oral gavage to time-mated Crl:CD®(SD) female rats (22 per dose group) on gestation days 6–20. Gavage doses in 0.5% aqueous methyl cellulose were 0, 20, 100, 300 and 1000 mg/kg bw per day. The dosing volume was 5 mL/kg bw. Parameters evaluated in dams were body weight, body weight gain (absolute and adjusted for the products of conception), feed consumption, survival, clinical signs, reproductive outcomes and gross pathology. Parameters evaluated in fetuses were body weight, incidences of dead fetuses and/or fetal resorptions, and incidences of external, visceral, head and skeletal malformations and variations.

No test substance–related effects on maternal clinical observations, body weight, body weight gain, feed consumption or gross postmortem observations were observed at any dose level. Unscheduled mortality did not occur. The mean numbers of corpora lutea, implantation sites, resorptions and live fetuses, fetal weight and sex ratio were comparable across all groups. There were no test substance–related fetal external, visceral or skeletal malformations or variations.

The NOAELs for both maternal and embryo/fetal toxicity in rats were 1000 mg/kg bw per day, the highest dose tested (Munley, 2009a).

Rabbits

In a developmental toxicity study, cyantraniliprole (purity 94.5%; batch no. HGW86-230) was administered by oral gavage to time-mated Hra:(NZW)SPF female rabbits (22 per group) on gestation days 7–28. Gavage doses in 0.5% aqueous methyl cellulose were 0, 25, 100, 250 and 500 mg/kg bw per day. The dosing volume was 5 mL/kg bw. Parameters evaluated in dams were body weight, body weight gain (absolute and adjusted for the products of conception), feed consumption, survival, clinical signs, reproductive outcomes and gross pathology. Parameters evaluated in fetuses were body weight, incidences of dead fetuses and/or fetal resorptions, and incidences of external, visceral and skeletal malformations and variations.

Evidence of maternal toxicity was observed at 100 mg/kg bw per day and above and included increased clinical signs of toxicity, including diarrhoea, and lower body weights and feed consumption. Maternal toxicity was sufficiently severe to result in the early euthanasia of two does at 100 mg/kg bw per day. At 250 and 500 mg/kg bw per day, abortions in late gestation and/or deliveries on the day of scheduled termination occurred in three does at 500 mg/kg bw per day and four does at 250 mg/kg bw per day. The abortions/deliveries were considered to be secondary effects of the adverse maternal toxicity that was observed at these doses. Treatment-related effects on offspring were limited to test substance–related reductions in mean fetal weight at 250 and 500 mg/kg bw per day. The lower fetal weight was considered to be related to the severe decrease in maternal body weight gain at 250 mg/kg bw per day and above.

The NOAEL for maternal toxicity in rabbits was 25 mg/kg bw per day, based on mortality, increased clinical signs of toxicity, including diarrhoea, and lower body weights and feed consumption at 100 mg/kg bw per day. The NOAEL for embryo and fetal toxicity in rabbits was 100 mg/kg bw per day, based on reductions in fetal weight at 250 mg/kg bw per day (Munley, 2009b).

2.6 Special studies

(a) Neurotoxiciy

Acute oral neurotoxicity study in rats

In an acute neurotoxicity study, cyantraniliprole (purity 93.4%; batch no. HGW86-141) was administered to male and female Crl:CD®(SD)IGS BR rats (12 of each sex per dose) by single-dose oral gavage in polyethylene glycol (PEG 400). Doses were 0, 250, 1000 and 2000 mg/kg bw. The dosing volume was 4 mL/kg bw. A neurobehavioural test battery, consisting of motor activity and functional observational battery assessments, was conducted on all study rats prior to dosing, approximately 2 hours after dosing (day 1) and on days 8 and 15. Other parameters evaluated included body weight, body weight gain and clinical signs. On test day 17, six rats of each sex per group were perfused in situ with fixative. A microscopic neuropathological evaluation of the peripheral and central nervous systems and selected muscle tissues from control and high-dose rats was conducted.

There were no treatment-related changes in body weight, body weight gain, feed consumption, feed efficiency, mortality, clinical observations, forelimb or hindlimb grip strength, hindlimb foot splay, body temperature, rearing, duration or number of movements, or any of the other behavioural parameters evaluated in the functional observational battery in either males or females administered any dose of the test substance. In addition, there were no gross or microscopic changes related to the treatment in the nervous system tissues.

The NOAEL for acute neurotoxicity in rats was 2000 mg/kg bw, the highest dose tested (Malley, 2006).

Ninety-day neurotoxicity study in rats

In a 90-day neurotoxicity feeding study, cyantraniliprole (purity 94.5%; batch no. HGW86-230) was administered to male and female Crl:CD®(SD) rats (12 of each sex per group) in the diet at a concentration of 0, 200, 2000 or 20 000 ppm (equal to 0, 11.4, 115 and 1195 mg/kg bw per day for males and 0, 14.0, 137 and 1404 mg/kg bw per day for females, respectively). Parameters evaluated included body weight, body weight gain, feed consumption, feed efficiency, clinical signs and gross pathology. A neurobehavioural test battery consisting of motor activity and functional observational battery assessments was conducted on 12 rats of each sex per group prior to the 1st day of dietary administration and during weeks 4, 8 and 13. On test days 92 and 93, six rats of each sex per group were perfused in situ with fixative. The peripheral and central nervous systems and selected muscle tissues from control and high-concentration rats (six rats of each sex per group) were prepared for histopathological evaluation to detect neurotoxicity.

There were no test substance–related effects on body weight, body weight gain, feed consumption, feed efficiency, clinical signs of toxicity, survival, neurobehavioural parameters, or gross and microscopic morphology of the nervous system in either male or female rats administered up to 20 000 ppm of test substance in the diet.

The NOAEL for neurotoxicity and systemic toxicity in rats was 20 000 ppm (equal to 1195 mg/kg bw per day), the highest dose tested, based on the absence of adverse effects of the test substance at this dose (Mukerji, 2009).

(b) Immunotoxicity

Twenty-eight-day dietary immunotoxicity study in mice

In a 28-day immunotoxicity feeding study, cyantraniliprole (purity 94.5%; batch no. HGW86-0603-1) was administered to male and female Crl:CD1®(ICR) mice (10 of each sex per group) at a concentration of 0, 20, 150, 1000 or 7000 ppm (equal to 0, 3.0, 23, 154 and 1065 mg/kg bw per day for males and 0, 4.1, 32, 224 and 1386 mg/kg bw per day for females, respectively). Body weights, feed consumption measurements and clinical observations were recorded during the in-life period. Prior to sacrifice, the immune system was stimulated by injecting sheep red blood cells (sRBCs) on test day 23 or 24, and blood samples were collected from each mouse on test day 28 or 29. The serum samples were assayed for their concentrations of sRBC-specific immunoglobulin M (IgM) antibodies to provide a quantitative assessment of humoral immune response. Serum from animals similarly challenged with a positive control immunosuppressive agent was analysed concurrently to provide confirmation that the assay performance was acceptable for detection of immunosuppression. At sacrifice, each animal was examined grossly, and selected organs were weighed (brain, spleen and thymus).

There were no adverse effects on body weight or nutritional parameters in male or female mice at any dose level. No clinical signs of systemic toxicity were observed. No adverse effects were observed on gross pathology, absolute and relative brain, spleen and thymus weights, or humoral immune response.

The NOAEL for immunotoxicity in mice was 7000 ppm (equal to 1065 mg/kg bw per day), the highest concentration tested (Hoban, 2011).

Twenty-eight-day dietary immunotoxicity study in rats

In a 28-day immunotoxicity feeding study, cyantraniliprole (purity 94.5%; batch no. HGW86-0603-1) was administered to male and female Crl:CD®(SD) rats (10 of each sex per concentration) at a concentration of 0, 20, 200, 2000 or 20 000 ppm (equal to 0, 1.7, 17, 166 and 1699 mg/kg bw per day for males and 0, 1.8, 18, 172 and 1703 mg/kg bw per day for females, respectively). Body weights, feed consumption measurements and clinical observations were recorded during the in-life period. Prior to sacrifice, the immune system was stimulated by injecting sRBCs on test day 22 for males or 23 for females, and blood samples were collected from each rat on test day 28 for males or 29 for females. The serum samples were assayed for their concentration of sRBC-specific IgM

antibodies to provide a quantitative assessment of humoral immune response. Serum from animals similarly challenged with a positive control immunosuppressive agent were analysed concurrently to provide confirmation that the assay performance was acceptable for detection of immunosuppression. At sacrifice, each animal was examined grossly, and selected organs were weighed (brain, spleen and thymus).

There were no adverse effects on body weight or nutritional parameters in male or female rats at any dose level. No clinical signs of systemic toxicity were observed. No adverse effects were observed on gross pathology, absolute and relative brain, spleen and thymus weights, or humoral immune response.

The NOAEL for immunotoxicity in rats was 20 000 ppm (equal to 1699 mg/kg bw per day), the highest concentration tested (Hoban, 2009b).

(c) Mechanistic study of thyroid effects

In vitro study of thyroid peroxidase inhibition

Thyroid peroxidase catalyses the first two steps in thyroid hormone synthesis, oxidation of iodide to iodine and the iodination of tyrosine residues on thyroglobulin. Severe inhibition of thyroid peroxidase affects the homeostasis of the hypothalamic–pituitary–thyroid axis. The objective of this study was to evaluate the ability of cyantraniliprole (purity 94.5%; batch no. HGW86-230) to inhibit thyroid peroxidase activity in vitro using thyroid preparations from the Yucatan pig (microswine). Cyantraniliprole concentrations ranged from 2 to 400 µmol/L, the maximum concentration being the limit of solubility in the assay system. Propylthiouracil (PTU), a substance known to inhibit thyroid peroxidase, was used as a positive control to verify test system performance. The concentration that caused a 50% reduction in enzyme activity (IC_{50}) for PTU was 7.3 µmol/L. Cyantraniliprole did not cause inhibition of thyroid peroxidase at any concentration tested when using guaiacol as the substrate; therefore, it was not possible to determine an IC_{50} value for cyantraniliprole. Under the conditions of this in vitro study, cyantraniliprole at concentrations up to 400 µmol/L did not inhibit thyroid peroxidase activity (Snajdr, 2010).

In vivo study of thyroid changes

A study was performed to evaluate potential mechanisms of thyroid gland changes following exposure of rats to cyantraniliprole. Two groups of young adult female Crl:CD®(SD) rats (15 per group) were fed control diet or diet containing 20 000 ppm (equal to 1903 mg/kg bw per day) cyantraniliprole (purity 94.5%; batch no. HGW86-230) for 29 days. Body weights, feed consumption and feed efficiency were evaluated weekly, and clinical observations were evaluated daily. Thyroid-related end-points (hormone measurements, anatomic pathology, organ weights and hepatic biochemistry) were evaluated. Females were used, as this was the sex more sensitive to effects on these parameters in previous studies.

No effects on mean feed consumption, mortality or clinical observations were observed. Female rats fed 20 000 ppm cyantraniliprole in the diet had lower body weight, body weight gain and feed efficiency compared with controls. Increased liver and thyroid weights and minimal thyroid follicular cell hypertrophy were induced by 29 days of treatment. These effects were associated with increased hepatic UDPGT activity and alterations in thyroid hormone homeostasis, including reduced serum T_4 concentration and increased TSH levels. These effects support increased clearance of T_4 due to increased induction of UDPGT in the liver, leading to lower T_4 levels, activated negative feedback on the hypothalamus and pituitary and subsequent increased TSH stimulation of the thyroid gland, as the predominant mechanism of the observed thyroid follicular cell hypertrophy. A reduction in hepatic microsomal 5′-deiodinase activity was also observed, but there were no effects on T_3 or reverse T_3 (rT_3) levels (MacKenzie, 2010b).

Based on the mechanistic studies described above, the effect of cyantraniliprole on thyroid follicles is considered to be secondary due to excess excretion of thyroid hormones from blood by

treatment-related induction of drug metabolism enzymes in the liver (Hill et al., 1989; Capen, 1997), but the biological significance of the reduction in hepatic microsomal metabolism enzymes was unclear due to the absence of any difference in T_3 or rT_3 levels.

It is well established that rats are more sensitive than dogs or primates (including humans) to thyroid hormone perturbations; the difference in sensitivity is likely due to the difference in half-life of the thyroid hormones, which is considerably shorter in the rat. This difference is due to the presence of thyroxine binding globulin in humans, which is not present in rats. Differences in plasma half-life are considered to be one of the primary reasons the rat, unlike humans, is prone to developing thyroid tumours as a result of TSH stimulation (Capen, 1997; Tucker, 1998). Therefore, this type of effect on the thyroid gland in rats is not considered relevant to human risk assessment.

(d) Mechanistic study of adrenal changes

Mice

A study was performed in mice to evaluate the impact of cyantraniliprole exposure on adrenal gland function and ultrastructure. Two groups of young adult male Crl:CD1® mice (10 per group) were fed control diet or diet containing 7000 ppm cyantraniliprole (purity 91.5%; batch no. HGW86-141) (equal to 1120 mg/kg bw per day) for 93 days. Body weights and feed consumption were evaluated weekly, and clinical observations were evaluated daily. At week 12, urine corticosterone, urine volume and creatinine were measured using an overnight collection of urine. After 93 days of exposure, mice were euthanized, and adrenal glands were weighed and collected. The right adrenal gland was evaluated microscopically from all mice. Left adrenal glands from four mice per group were used for electron microscopic examination.

No treatment-related clinical signs were detected. Body weight gain and feed intakes were decreased in the treated group. No treatment-related effects on histopathology, including ultrastructure in the adrenal cortex cells, urine analysis or hormone assays of corticosterone, were observed (MacKenzie, 2010a).

Rats

Three groups of young adult male Crl:CD®(SD) rats (10 per group) were fed control diet (groups 1 [adrenocorticotrophic hormone (ACTH)–stimulated] and 3 [non-ACTH-simulated]) or diet containing 20 000 ppm of cyantraniliprole (purity 94.5%; batch no. HGW86-230) (group 2), equal to 1230 mg/kg bw per day, for 93 days. The ACTH stimulation test is a well established clinical procedure in human and veterinary medicine that evaluates the responsiveness of the adrenal cortex to ACTH. For this test, exogenous ACTH is administered to simulate conditions of physiological stress, and the adrenal cortical response is evaluated by measuring serum glucocorticoid concentrations. In addition, body weights, feed consumption and feed efficiency were evaluated weekly, and clinical observations were evaluated daily. Adrenal end-points (urine corticosterone, adrenal response to ACTH, organ weights and pathology, including electron microscopic examination) were evaluated in males only, because males were previously observed to be more sensitive than females to these respective effects.

No adverse effects were observed on mean body weight gain or feed efficiency in male rats or on mean feed consumption, mortality or clinical observations. In radioimmunoassay, basal urinary corticosterone and ACTH-induced serum corticosterone levels were comparable to levels in the control group (Table 25). Daily dietary exposure at 20 000 ppm for 93 days resulted in increased microvesiculation of the adrenal cortex, with no evidence of cytotoxicity or degeneration. In electron microscopic examination, a minimal to mild increase in lipid vacuoles was observed in the cytoplasm of fascicular zone cells, but no effects on cellular organelles or evidence of cytotoxicity or degeneration was detected. The results indicate that the increased microvesiculation in fascicular zone cells in the adrenal cortex was not associated with changes in adrenal cortical function (MacKenzie, 2010b).

Table 25. Summary of effects on the adrenal in male rats

	0 ppm	20 000 ppm	0 ppm
No. of rats examined	10[a]	10	10
Before treatment with ACTH (day 86)			
Treatment with ACTH (12.5 µg/rat, intravenous)	No	No	No
Urine volume	6.7	9.4	NE
Urine creatinine (ng/mL × 10^4)	181	150	NE
Urine corticosterone (ng/mL)	84.2	87.3	NE
After treatment with ACTH (day 93)			
Treatment with ACTH (12.5 µg/rat, intravenous)	Yes	Yes	No
Serum corticosterone (ng/mL)	410	473	87[b]
Histopathology: Increased microvesiculation in fascicular zone cell, minimal	0	4	0

ACTH: adrenocorticotrophic hormone; NE, not examined
[a] Number of rats for measurement of serum corticosterone level was 9.
[b] No increase in serum corticosterone level after ACTH treatment in the control group.
Source: MacKenzie (2010b)

Based on the results from the above two mechanistic studies, mild increased microvesiculation of fascicular zone cells in the adrenal cortex and increased small lipid droplets in the cytoplasm in rats and mice in short-term studies and the reproductive toxicity study in rats were considered to be treatment related but not adverse and within normal physiological limits (MacKenzie, 2010a,b).

3. Studies on metabolites and/or degradates

Acute toxicity and genotoxicity studies on the metabolites and/or degradates of cyantraniliprole from high-temperature food processing (IN-JSE76 and IN-PLT97) and the degradates of cyantraniliprole in soil (IN-N5M09 and IN-F6L99) were conducted. A 28-day toxicity study on IN-JSE76 was conducted in rats.

3.1 Acute toxicity

Acute toxicity studies of cyantraniliprole metabolites and/or degradates are summarized in Table 26.

Table 26. Acute toxicity of cyantraniliprole metabolites and/or degradates

Metabolite/degradate (purity; batch no.)	Species	LD_{50} (mg/kg bw)	Clinical signs	Reference
IN-JSE76 (purity 93.8%; batch no. IN-JSE76-005)	Female SD rats (6/group)	> 5 000	No deaths or clinical signs	Oley (2009)
IN-PLT97 (purity 98.1%; batch no. E115107-77B)	Three female mice	> 5 000	No deaths or clinical signs	Carpenter (2010a)
IN-F6L99 (purity 98.6%; batch no. 004)	Three female mice treated with 2 000 mg/kg bw; one mouse treated with 175 or 550 mg/kg bw	> 2 000	No deaths or clinical signs	Finlay (2006)
IN-N5M09 (purity 99.9%; batch no. D100855-058)	Three female mice treated with 5 000 mg/kg bw	> 5 000	No deaths or clinical signs	Carpenter (2010b)

LD_{50}: median lethal concentration

3.2 Short-term studies of toxicity

In a 28-day feeding study, IN-JSE76 (purity 97.8%; batch no. IN-JSE76-005) was administered to male and female Crl:CD®(SD) rats (10 of each sex per group) at a dietary concentration of 0, 100, 400, 3000 or 20 000 ppm (equal to 0, 7, 29, 212 and 1445 mg/kg bw per day for males and 0, 8, 31, 232 and 1471 mg/kg bw per day for females, respectively). Parameters evaluated included body weight, body weight gain, feed consumption, feed efficiency, clinical signs, serum thyroid hormone levels, hepatic microsomal and peroxisomal enzymes (cytochrome P450, β-oxidation and UDPGT), gross pathology, organ weights, haematology, clinical chemistry, urine analysis and histopathology. Blood (from non-fasted animals) was collected on test days 23 (males) and 24 (females) for analysis of the concentration of IN-JSE76 and selected other metabolites in plasma.

No deaths occurred, and no clinical or ophthalmological observations were attributed to exposure to the test substance. No test substance–related effects on body weight or any nutritional parameters were observed. There were no adverse effects on any clinical pathology parameters (haematology, clinical chemistry, coagulation, urine analysis), organ weights or pathology findings related to treatment. In male rats, serum T_4 levels were statistically significantly decreased at 400, 3000 and 20 000 ppm. Although not significant, there were also corresponding increases in TSH levels at 3000 and 20 000 ppm. These changes were considered to be treatment related, but not adverse, due to the lack of corresponding organ weight and microscopic findings.

The plasma concentrations of IN-JSE76 were approximately linear with respect to dose in both male and female rats over the range of doses tested. There was no sex difference in the plasma concentration of IN-JSE76. The only targeted metabolite that had quantifiable levels in plasma was IN-K5A78, which was reported for the highest-dose group in females and in the two highest-dose groups in males.

The NOAEL for short-term toxicity of IN-JSE76 in rats was 20 000 ppm (equal to 1445 mg/kg bw per day), the highest dose tested (Anand, 2010; Mawn, 2011).

3.3 Genotoxicity

Genotoxicity studies on cyantraniliprole metabolites and/or degradates are summarized in Table 27.

4. Observations in humans

No information on medical surveillance or poisoning incidents was available.

Comments

Biochemical aspects

Cyantraniliprole is readily absorbed in rats, and the absorption is higher at 10 mg/kg bw than at 150 mg/kg bw. The majority of the absorption occurs during the first 48 hours (80% of the absorbed radioactivity), and the peak plasma concentration (C_{max}) is reached approximately 2 hours after dosing, regardless of the sex or dose level. The C_{max} and AUC values demonstrate a 2- to 3-fold greater exposure in female rats than in male rats. Following oral dosing, the majority of the dose is extensively distributed throughout the body. The half-life is shorter in male rats than in female rats (42–54 hours in males and 117–129 hours in females). The absorbed cyantraniliprole is readily and extensively metabolized, mainly by hydroxylation of methylphenyl and *N*-methyl carbon. Further metabolism of the hydroxylated metabolites includes *N*-methylation, nitrogen-to-carbon cyclization with loss of a water molecule, oxidation of alcohols to carboxylic acids, amide bridge cleavage, amine hydrolysis and *O*-glucuronidation. The bile is found to be very rich in metabolites, and most of the metabolites are found in both urine and faeces. IN-MLA84 (2-[3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-1,4-dihydro-8-methyl-4-oxo-6-quinazoline carbonitrile) is the most abundant

Table 27. Summary of genotoxicity studies of cyantraniliprole metabolites and/or degradates

Metabolite (purity; batch no.)	Type of study	Test system	Concentration range tested	Result	Reference
IN-JSE76 (purity 93.8%; batch no. JSE76-005)	In vitro bacterial mutagenicity (Ames)	*Salmonella typhimurium* and *Escherichia coli*	50–5 000 µg/plate (±S9)	Negative	Wagner & VanDyke (2009b)
IN-JSE76 (purity 93.8%; batch no. JSE76-005)	In vitro chromosomal aberration (clastogenicity)	Human lymphocytes	313–2 500 µg/mL (4 h, −S9) 156–2 500 µg/mL (4 h, +S9) 156–2 000 µg/mL (20 h, −S9)	Negative	Gudi & Rao (2010)
IN-JSE76 (purity 93.8%; batch no. JSE76-005)	In vitro mammalian cell mutagenicity (CHO/HPRT)	CHO cells	100–1 500 µg/mL (±S9)	Negative	Clarke (2009)
IN-PLT97 (purity 98.1%; batch no. PLT97-003)	In vitro bacterial mutagenicity (Ames)	*S. typhimurium* and *E. coli*	50–5 000 µg/plate (±S9)	Negative	Wagner & Jois (2010)
IN-PLT97 (purity 98.1%; batch no. PLT97-003)	In vitro chromosomal aberration (clastogenicity)	Human lymphocytes	25–1 550 µg/mL (4 h, ±S9) 25–1 550 µg/mL (20 h, −S9)	Negative	Madraymootoo & Jois (2011)
IN-PLT97 (purity 98.1%; batch no. PLT97-003)	In vitro mammalian cell mutagenicity (CHO/HPRT)	CHO cells	10–150 µg/mL (±S9)	Negative	Clarke (2010)
IN-F6L99 (purity 98.6%; batch no. F6L99-004)	In vitro bacterial mutagenicity (Ames)	*S. typhimurium* and *E. coli*	33.3–5 000 µg/plate (±S9)	Negative	Wagner & Jois (2010)
IN-N5M09 (purity 99.9%; batch no. N5M09-003)	In vitro bacterial mutagenicity (Ames)	*S. typhimurium* and *E. coli*	1.5–5 000 µg/plate (±S9)	Negative	Wagner & VanDyke (2009c)

CHO: Chinese hamster ovary; HPRT: hypoxanthine–guanine phosphoribosyltransferase; S9: 9000 × *g* supernatant fraction of rat liver homogenate

analyte in the blood of rats and mice of both sexes, whereas the highest concentrations in dogs are of the parent compound, cyantraniliprole.

Toxicological data

In rats, the oral LD_{50} was greater than 5000 mg/kg bw, the dermal LD_{50} was greater than 5000 mg/kg bw and the inhalation LC_{50} was greater than 5.2 mg/L. Cyantraniliprole was not a skin irritant in rabbits, an eye irritant in rabbits or a skin sensitizer.

Liver was the interspecies target of cyantraniliprole in short- and long-term studies, although dogs appeared to be more sensitive than rats. In rodents, the thyroid was also a target organ, with adverse effects on thyroid hormone metabolism.

Short-term toxicity of cyantraniliprole was examined in mice, rats and dogs. The NOAEL in a 28-day oral toxicity study in mice was 7000 ppm (equal to 1261 mg/kg bw per day), the highest dose tested. The NOAEL in a 90-day oral toxicity study in which mice were administered cyantraniliprole in the diet at a concentration of 0, 50, 300, 1000 or 7000 ppm (equal to 0, 7.2, 47.1, 150 and 1092 mg/kg bw per day for males and 0, 9.7, 58.1, 204 and 1344 mg/kg bw per day for females,

respectively) was 1000 ppm (equal to 204 mg/kg bw per day), based on minimal necrosis in the liver at 7000 ppm (equal to 1344 mg/kg bw per day) in females.

In a 28-day oral toxicity study in which rats were administered cyantraniliprole in the diet at a concentration of 0, 600, 2000, 6000 or 20 000 ppm (equal to 0, 53, 175, 528 and 1776 mg/kg bw per day for males and 0, 62, 188, 595 and 1953 mg/kg bw per day for females, respectively), the NOAEL was 600 ppm (equal to 53 mg/kg bw per day), based on liver hypertrophy and thyroid follicular cell hypertrophy observed in both sexes at 2000 ppm (equal to 175 mg/kg bw per day). In a 90-day oral toxicity study in which rats were administered a dietary concentration of 0, 100, 400, 3000 or 20 000 ppm (equal to 0, 5.7, 22, 168 and 1147 mg/kg bw per day for males and 0, 6.9, 27, 202 and 1346 mg/kg bw per day for females, respectively), the NOAEL was 100 ppm (equal to 5.7 mg/kg bw per day), based on liver hypertrophy, decreases in thyroid hormones in both sexes and histopathological changes in the thyroid in females at 400 ppm (equal to 22 mg/kg bw per day).

Three feeding studies (28 days, 90 days and 1 year) were conducted with cyantraniliprole in dogs. A NOAEL for the 28-day oral toxicity study in dogs was not determined, based on changes in body weight, nutritional parameters and clinical chemistry indicating hepatotoxicity in both sexes at 1000 ppm (equal to 35 mg/kg bw per day), the lowest dose tested. The NOAEL for the 90-day oral toxicity study in which dogs were administered cyantraniliprole at 0, 30, 100, 1000 or 10 000 ppm (equal to 0, 0.98, 3.08, 31.9 and 281 mg/kg bw per day for males and 0, 0.97, 3.48, 34.3 and 294 mg/kg bw per day for females, respectively) was 100 ppm (equal to 3.08 mg/kg bw per day), based on increased total protein, albumin and AP levels in males at 1000 ppm (equal to 31.9 mg/kg bw per day). In a 1-year dog study utilizing concentrations of 0, 40, 200, 1000 and 5000 ppm (equal to 0, 0.96, 5.67, 27.0 and 144 mg/kg bw per day for males and 0, 1.12, 6.00, 27.1 and 133 mg/kg bw per day for females, respectively), the increased levels of AP at 40 ppm were not considered adverse in view of the absence of histopathological or functional changes at this and the next higher dose (200 ppm). Therefore, the NOAEL for the 1-year oral toxicity study in dogs was 40 ppm (equal to 0.96 mg/kg bw per day), based on marginal increases in AP levels without histopathological change in the liver in both sexes, increased liver weights in males and decreased cholesterol in females at 200 ppm (equal to 5.67 mg/kg bw per day). The Meeting concluded that the overall NOAEL for oral toxicity in dogs was 100 ppm (equal to 3.08 mg/kg bw per day), and the overall lowest-observed-adverse-effect level (LOAEL) was 200 ppm (equal to 5.67 mg/kg bw per day).

Long-term toxicity studies were conducted in mice and rats. In an 18-month carcinogenicity study in which mice were administered a dietary concentration of 0, 20, 150, 1000 or 7000 ppm (equal to 0, 2.0, 15.5, 104 and 769 mg/kg bw per day for males and 0, 2.4, 18.6, 131 and 904 mg/kg bw per day for females, respectively), the NOAEL for toxicity was 1000 ppm (equal to 104 mg/kg bw per day), based on a decrease in body weight gain and increased thyroid weight in males at 7000 ppm (equal to 769 mg/kg bw per day). No increase in neoplastic incidence was observed. The NOAEL for carcinogenicity in mice was 7000 ppm (equal to 769 mg/kg bw per day), the highest dose tested.

In a 2-year toxicity and carcinogenicity feeding study in which rats were administered cyantraniliprole in the diet at 0, 20, 200, 2000 or 20 000 ppm (equal to 0, 0.8, 8.3, 84.8 and 907 mg/kg bw per day for males and 0, 1.1, 10.5, 107 and 1161 mg/kg bw per day for females, respectively), the NOAEL for toxicity was 200 ppm (equal to 8.3 mg/kg bw per day), based on increased incidences of foci of cellular alteration in the liver in males and hepatocellular vacuolation in both sexes and slight depression of body weights in females at 2000 ppm (equal to 84.8 mg/kg bw per day). No increase in neoplastic incidence was observed, and the NOAEL for carcinogenicity in rats was 20 000 ppm (equal to 907 mg/kg bw per day), the highest dose tested.

The Meeting concluded that cyantraniliprole is not carcinogenic in mice or rats.

Cyantraniliprole was tested for genotoxicity in vitro and in vivo in an adequate range of assays. In these assays, there was no evidence of genotoxic potential.

The Meeting concluded that cyantraniliprole is unlikely to be genotoxic.

On the basis of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that cyantraniliprole is unlikely to pose a carcinogenic risk to humans.

In a multigeneration reproductive toxicity study in which rats were given cyantraniliprole at a concentration of 0, 20, 200, 2000 or 20 000 ppm (in P generation: equal, respectively, to 0, 1.1, 11.0, 110 and 1125 mg/kg bw per day for males, 0, 1.4, 13.9, 136 and 1344 mg/kg bw per day for premating females, 0, 1.4, 13.3, 135 and 1353 mg/kg bw per day for females during gestation, and 0, 2.7, 27.0, 283 and 2782 mg/kg bw per day for females during lactation; in F_1 generation: equal, respectively, to 0, 1.4, 14.6, 151 and 1583 mg/kg bw per day for males, 0, 1.9, 20.1, 203 and 2125 mg/kg bw per day for premating females, 0, 1.4, 14.7, 149 and 1518 mg/kg bw per day for females during gestation and 0, 2.7, 27.4, 277 and 2769 mg/kg bw per day for females during lactation), the NOAEL for parental toxicity was 200 ppm (equal to 11.0 mg/kg bw per day), based on hepatocellular hypertrophy and thyroid follicular cell hypertrophy in both sexes at 2000 ppm (equal to 110 mg/kg bw per day) in the P generation. The NOAEL for reproductive toxicity was 20 000 ppm (equal to 1344 mg/kg bw per day), the highest dose tested. The NOAEL for offspring toxicity was 2000 ppm (equal to 280 mg/kg bw per day, mean value for P and F_1 parental females during lactation), based on lower body weights of F_1 and F_2 generation pups at 20 000 ppm (equal to 2776 mg/kg bw per day, mean value for P and F_1 parental females during lactation).

In a developmental toxicity study in rats administered a dose of 0, 20, 100, 300 or 1000 mg/kg bw per day, the NOAELs for both maternal and embryo/fetal toxicity in rats were 1000 mg/kg bw per day, the highest dose tested.

In a developmental toxicity study in rabbits administered a dose of 0, 25, 100, 250 or 500 mg/kg bw per day, the NOAEL for maternal toxicity was 25 mg/kg bw per day, based on mortality, increased clinical signs of toxicity, including diarrhoea, and lower body weights and feed consumption at 100 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 100 mg/kg bw per day, based on reductions in fetal weight at 250 mg/kg bw per day.

The Meeting concluded that cyantraniliprole is not teratogenic in rats or rabbits.

In an acute neurotoxicity study in rats, the NOAEL was 2000 mg/kg bw, the highest dose tested.

In a 90-day study of neurotoxicity in which rats were administered a dose of 0, 200, 2000 or 20 000 ppm (equal to 0, 11.4, 115 and 1195 mg/kg bw per day for males and 0, 14.0, 137 and 1404 mg/kg bw per day for females, respectively), the NOAEL was 20 000 ppm (equal to 1195 mg/kg bw per day), the highest dose tested.

The Meeting concluded that cyantraniliprole is not neurotoxic.

Immunotoxicity studies were conducted in mice and rats. In a 28-day immunotoxicity study in mice, the NOAEL was 7000 ppm (equal to 1065 mg/kg bw per day), the highest dose tested. In a 28-day immunotoxicity study in rats, the NOAEL was 20 000 ppm (equal to 1699 mg/kg bw per day), the highest dose tested.

Toxicological data on metabolites and/or degradates

Acute toxicity and genotoxicity studies of metabolites and/or degradates were conducted. 4-[[[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-3-methyl-5-[(methylamino)-carbonyl]benzoic acid (IN-JSE76), 2-[3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-1,4-dihydro-8-methyl-4-oxo-6-quinazolinecarboxylic acid (IN-PLT97), 6-chloro-4-methyl-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-2-carbonitrile (IN-N5M09) and 3-bromo-*N*-methyl-1*H*-pyrazole-5-carboxamide (IN-F6L99) were degradates in soil. All metabolites and/or degradates exhibited low acute toxicities and no genotoxicity. The NOAEL in a 28-day toxicity study of IN-JSE76 in rats was 20 000 ppm (equal to 1445 mg/kg bw per day), the highest dose tested.

Human data

No information on medical surveillance or poisoning incidents was available.

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.03 mg/kg bw on the basis of the overall NOAEL of 3.08 mg/kg bw per day in dog studies, based on liver effects at 5.67 mg/kg bw per day. A safety factor of 100 was applied.

The metabolites IN-N7B69, IN-MLA84, IN-MYX98 and IN-J9Z38 have been included in the residue definition. As the estimated exposure to IN-N7B69 is below the threshold of toxicological concern for Cramer class III compounds, there is no concern for this metabolite. For the other three metabolites, these have been tested in rodents through their formation from the parent compound and are therefore covered by the ADI for cyantraniliprole.

The Meeting concluded that it was not necessary to establish an acute reference dose (ARfD) for cyantraniliprole in view of its low acute toxicity and the absence of developmental toxicity and any other toxicological effects that would be likely to be elicited by a single dose.

Levels relevant to risk assessment of cyantraniliprole

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity[a]	Toxicity	1 000 ppm, equal to 104 mg/kg bw per day	7 000 ppm, equal to 769 mg/kg bw per day
		Carcinogenicity	7 000 ppm, equal to 769 mg/kg bw per day[b]	–
Rat	Ninety-day study of toxicity[a]	Toxicity	100 ppm, equal to 5.7 mg/kg bw per day	400 ppm, equal to 22 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	200 ppm, equal to 8.3 mg/kg bw per day	2 000 ppm, equal to 84.8 mg/kg bw per day
		Carcinogenicity	20 000 ppm, equal to 907 mg/kg bw per day[b]	–
	Multigeneration reproductive toxicity study[a]	Parental toxicity	200 ppm, equal to 11.0 mg/kg bw per day	2 000 ppm, equal to 110 mg/kg bw per day
		Reproductive toxicity	20 000 ppm, equal to 1 344 mg/kg bw per day[b]	–
		Offspring toxicity	2 000 ppm, equal to 280 mg/kg bw per day	20 000 ppm, equal to 2 776 mg/kg bw per day
	Developmental toxicity study[c]	Maternal toxicity	1 000 mg/kg bw per day[b]	–
		Embryo and fetal toxicity	1 000 mg/kg bw per day[b]	–
	Acute neurotoxicity	Toxicity	2 000 mg/kg bw per day[b]	–
	Ninety-day study of neurotoxicity[a]	Neurotoxicity	20 000 ppm, equal to 1 195 mg/kg bw per day[b]	–

Species	Study	Effect	NOAEL	LOAEL
Rabbit	Developmental toxicity study[c]	Maternal toxicity	25 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	100 mg/kg bw per day	250 mg/kg bw per day
Dog	Ninety-day and 1-year studies of toxicity[a,d]	Toxicity	100 ppm, equal to 3.08 mg/kg bw per day	200 ppm, equal to 5.67 mg/kg bw per day

LOAEL: lowest-observed-adverse-effect level; NOAEL: no-observed-adverse-effect level
[a] Dietary administration.
[b] Highest dose tested.
[c] Gavage administration.
[d] Two or more studies combined.

Estimate of acceptable daily intake

0–0.03 mg/kg bw

Estimate of acute reference dose

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 cyantraniliprole

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid (in 2 h) and extensive (> 80%)
Dermal absorption	No data
Distribution	Extensive; all tissues
Potential for accumulation	Low
Rate and extent of excretion	Rapid (mainly in 48 h samples) and extensive; faeces > urine
Metabolism in animals	IN-MLA84 is abundant in mice and rats, less in dogs
Toxicologically significant compounds in animals, plants and the environment	Cyantraniliprole, IN-MLA84, IN-MYX98 and IN-J9Z38
Acute toxicity	
Rat, LD_{50}, oral	> 5 000 mg/kg bw
Rat, LD_{50}, dermal	> 5 000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.2 mg/L
Rat, dermal irritation	Non-irritating
Rabbit, ocular irritation	Non-irritating
Dermal sensitization	Non-sensitizing (LLNA in mice; maximization test in guinea-pigs)
Short-term toxicity	
Target/critical effect	Liver and thyroid / increases in AP and liver weights (dogs)
Lowest relevant oral NOAEL	3.08 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day (rat)

Lowest relevant inhalation NOAEC	No data
Long-term toxicity and carcinogenicity	
Target/critical effect	Liver and thyroid / increased incidence of altered foci of hepatocytes in the liver, decreased body weight gain in females
Lowest relevant NOAEL	8.3 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic
Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Reproduction target/critical effect	No reproductive toxicity
Lowest relevant parental NOAEL	11.0 mg/kg bw per day
Lowest relevant offspring NOAEL	280 mg/kg bw per day
Lowest relevant reproductive NOAEL	1 344 mg/kg bw per day, the highest dose tested
Developmental toxicity	
Target/critical effect	Mortality, increased clinical signs, decreased body weight gain and lower feed consumption of dams
Lowest relevant maternal NOAEL	25 mg/kg bw per day (rabbit)
Lowest relevant developmental NOAEL	100 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute and subchronic neurotoxicity	Not neurotoxic
Immunotoxicity	
Lowest relevant immunotoxicity NOAEL	1 065 mg/kg bw per day, the highest dose tested (mouse)
Medical data	
	No information available

LC_{50}: median lethal concentration; LD_{50}: median lethal dose; NOAEC: no-observed-adverse-effect concentration; NOAEL: no-observed-adverse-effect level

Summary

	Value	Study	Safety factor
ADI	0–0.03 mg/kg bw	Ninety-day and 1-year toxicity studies (dog)	100
ARfD	Unnecessary	–	–

ADI: acceptable daily intake; ARfD: acute reference dose

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