QUINCLORAC

First draft prepared by
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Explanation

Quinclorac is the International Organization for Standardization (ISO)–approved common name for 3,7-dichloroquinoline-8-carboxylic acid (International Union of Pure and Applied Chemistry), with Chemical Abstracts Service number 84087-01-4. It is a herbicide of the quinoline carboxylic acid class. The pesticidal mode of action is as a mimic of the plant hormone auxin.

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

All critical studies contained statements of compliance with good laboratory practice (GLP).

Initial production batches of quinclorac contained cinnoline impurities that were associated with positive results in genotoxicity studies. Improved production methods have reduced the levels of these impurities, and current batches are reported to contain cinnolines at concentrations below 1 part per million (ppm). The sponsor has confirmed that current technical quinclorac has a purity of greater

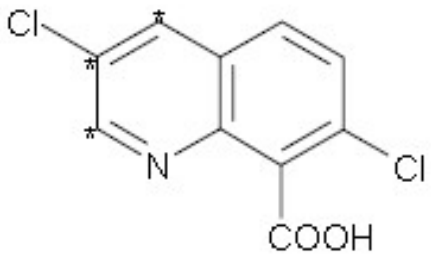
than 99% and that the material tested in the submitted toxicity studies adequately covers the impurities in current production material.

Evaluation for acceptable intake

1. Biochemical aspects

The structure of quinclorac and the position of the radiolabel used in the absorption, distribution, metabolism and excretion studies are shown in Fig. 1.

Fig. 1. Structure of quinclorac with position of radiolabel



* denotes the position of the radiolabel

The absorption, distribution, metabolism and excretion of quinclorac were investigated in a multicomponent study in CD rats (Hawkins et al., 1986). Groups of rats received [2,3,4-^{14}C]quinclorac (radiochemical purity 96.3%; specific activity 360.4 GBq/mol) by gavage in 1.5% aqueous methyl cellulose or in the diet. The dosing and investigation schedule is presented in Table 1. Samples of urine, faeces, bile, blood/plasma and tissues were obtained, processed and analysed by liquid scintillation counting (LSC) or whole-body autoradiography.

Table 1. Dose groups and investigations performed on rats receiving ^{14}C-labelled quinclorac

Group	Phase	No. of males	No. of females	Dose	Analyses performed
Gavage administration[a]					
1A	SOLD	5	5	15 mg/kg bw	Routes and rates of excretion and metabolite analysis in urine, faeces and carcass.
1B	SOHD	5	5	600 mg/kg bw	
1C	ROLD	5	5	14 daily cold doses of 15 mg/kg bw per day + a final radiolabelled dose of 15 mg/kg bw	Urine samples collected at 8, 24, 48, 72, 96 and 120 h. Faeces collected at 24, 48, 72, 96 and 120 h.
2A	SOLD Bile duct cannulated	3	3	15 mg/kg bw	Routes and rates of excretion and metabolite analysis in urine, bile, faeces and carcass.
2B	SOHD Bile duct cannulated	3	3	600 mg/kg bw	Urine and faeces collected at 24 and 48 h. Bile collected at 3 h intervals up to 48 h.
3A	Plasma TK	5	5	15 mg/kg bw	Plasma concentrations determined in blood

Group	Phase	No. of males	No. of females	Dose	Analyses performed
	(SOLD)				drawn at pre-dosing, 0.25, 0.5, 1, 2, 3, 5, 7, 24, (31, 3D only), 48, 72, 96, 120, 168 (not 3A) and 240 (not 3A) h post-dosing.
3B	Plasma TK	5	5	100 mg/kg bw	
3C	Plasma TK (SOHD)	5	5	600 mg/kg bw	
3D	Plasma TK	5	5	1 200 mg/kg bw	
3E	Plasma TK (ROLD)	5	5	7 daily radiolabelled doses of 15 mg/kg bw per day	Blood was drawn prior to the first and the last dose and at 0.25, 0.5, 1, 2, 3, 5, 7, 24, 48, 72, 96, 120, 168 and 240 h (+336 and 432 h for 3F) after the last dose.
3F	Plasma TK (ROHD)	5	5	7 daily radiolabelled doses of 600 mg/kg bw per day	
4A	Tissue accumulation	5	5	7 daily radiolabelled doses of 15 mg/kg bw per day	Pairs of rats (one of each sex) were killed at 0.5, 6, 24, 72 and 120 h after the final dose, and the liver, kidneys, heart, lungs, brain, eyes, testes, ovaries, spleen, pancreas, adrenals, thyroid, uterus, gastrointestinal tract and contents, bone marrow, muscle, fat, blood and plasma were analysed for radioactivity.
4B	Quantitative whole-body autoradiography	5	–	7 daily radiolabelled doses of 15 mg/kg bw per day	One animal was killed 24 h after the first dose, and additional single animals were sacrificed at 0.5, 6, 24, 72 and 120 h after the final dose. They were deep frozen, sectioned sagittally, dried and placed on photographic film.
Dietary administration					
5A	Plasma concentrations	3	3	Rats were offered diet containing 15 000 ppm radiolabelled material (~1 200 mg/kg bw) after 8 h of fasting	Blood was sampled pre-dosing and at 2, 9, 24, 42 and 66 h after dosing.
		3	3		Blood was sampled pre-dosing and at 4, 12, 24, 42 and 66 h after dosing.
		3	3		Blood was sampled pre-dosing and at 6, 18, 24, 42 and 66 h after dosing.
5B	Tissue accumulation	6	6	Rats were offered diet containing 15 000 ppm radiolabelled material (~1 200 mg/kg bw) for 7 days, after which it was replaced with untreated diet	Pairs of rats (one of each sex) were killed at 0.5, 6, 24, 72 and 120 h after withdrawal of the treated diet (one rat of each sex), and the liver, kidneys, heart, lungs, brain, eyes, testes, ovaries, spleen, pancreas, adrenals, thyroid, uterus, gastrointestinal tract and contents, bone marrow, muscle, fat, blood and plasma were analysed for radioactivity.

bw: body weight; ppm: parts per million; ROHD: repeated oral high dose; ROLD: repeated oral low dose; SOHD: single oral high dose; SOLD: single oral low dose; TK: toxicokinetics

[a] Gavage in 1.5% carboxymethyl cellulose.

Source: Hawkins et al. (1986, 1987)

1.1 Absorption, distribution and excretion

The extent of oral absorption was high (> 90%), based on urinary and biliary data, with most of the biliary component reabsorbed and excreted in urine (Table 2). The biliary component increased disproportionately with increasing dose from 15 to 600 mg/kg bw. Absorption of radiolabel was rapid,

Table 2. Excretion pattern in rats exposed to quinclorac

	Excretion after oral administration (% of dose)									
	SOLD		SOHD		ROLD		SOLD bile		SOHD bile	
	15 mg/kg bw		600 mg/kg bw		14 × 15 mg/kg bw		15 mg/kg bw		600 mg/kg bw	
	M	F	M	F	M	F	M	F	M	F
Bile 0–48 h	–	–	–	–	–	–	3	1	14	11
Urine 0–24 h	90	88	85	79	93	89	81	92	69	51
Urine (total)	94	94	96	98	95	91	85	94	80	63
Faeces 0–24 h	1	1	3	0.4	2	0.5	2	4	1	2
Faeces (total)	1	1	4	1	2	1	3	4	2	2
Total excretion	95	95	100	100	98	93	93	100	97	97

bw: body weight; F: females; M: males; ROLD: repeated oral low dose; SOHD: single oral high dose; SOLD: single oral low dose
Source: Hawkins et al. (1986)

with maximal blood concentrations achieved between 0.25 and 1 hour for single doses of 600 mg/kg bw and below (Table 3). Quinclorac was widely distributed in the body, with highest concentrations present in the blood, plasma and kidneys (Table 4). Tissue levels were generally higher (< 2-fold) in females than in males. The labelled material was rapidly excreted, primarily via urine (50–90% in 24 hours) (Table 2). Initial plasma half-lives were calculated to be approximately 3–4 hours. Clearance from the blood was slower following repeated dosing with 600 mg/kg bw and with single doses of 1200 mg/kg bw, resulting in non-proportionate increases in the area under the concentration–time curve (AUC) (Table 3). The excretion pattern and tissue distribution of radioactivity were similar across administered dose levels and when the administration of radiolabelled quinclorac was preceded by 7 or 14 days of administration of the labelled or unlabelled material (Hawkins et al., 1986, 1987).

1.2 Biotransformation

Samples obtained from the study of Hawkins et al. (1986) (described in section 1.1 above) were extracted and analysed for the presence of metabolites using techniques including thin-layer chromatography and mass spectroscopy. Absorbed quinclorac was metabolized to only a limited extent, with unchanged parent compound representing approximately 80% of the excreted radiolabel. The major biotransformation product was quinclorac–glucuronide conjugate, representing approximately 5% of the administered dose. The pattern of metabolism was similar across sexes, dose levels and administration of repeated doses. A number of metabolites each representing less than 5% of the administered dose were not identified (Hawkins et al., 1986, 1987).

The metabolism of quinclorac is so limited that a metabolic pathway is considered unnecessary.

2. Toxicological studies

2.1 Acute toxicity

(a) Lethal doses

Quinclorac was of low acute toxicity by the oral, dermal and inhalation routes (Table 5). In the acute oral toxicity studies, clinical signs (including dyspnoea, piloerection and poor general state) were seen at 1780 mg/kg bw and above.

Table 3. Plasma radioactivity levels and AUC in rats receiving ^{14}C-labelled quinclorac

	Plasma radioactivity (µg equiv/g)					
Time (h)	**SOLD 15 mg/kg bw**	**ROLD 15 mg/kg bw (7 days)**	**Single oral mid dose 100 mg/kg bw**	**SOHD 600 mg/kg bw**	**ROHD 600 mg/kg bw (7 days)**	**Single oral dose 1 200 mg/kg bw**
Males						
0.25	29	29	171	192	249	263
0.5	33	34	181	235	256	320
1	27	28	125	201	297	347
2	15	21	75	187	293	368
7	6	12	30	201	255	327
24	0.1	0.6	1.4	78	164	505
48	0.1	0.4	0.3	6	27	140
72	0.1	0.3	0.2	1.6	10	6
168	0.1	0.2	0.2	0.8	3	1
AUC (h·µg/mL)	*141*	*297*	*803*	*4 958*	*12 359*	*21 256*
Females						
0.25	32	41	134	188	194	274
0.5	33	39	168	247	239	320
1	24	27	142	224	226	328
2	11	13	514	201	293	368
7	2	3	28	181	210	198
24	0.2	0.3	2.1	73	110	268
48	0.1	0.3	1.6	11	31	319
72	0.1	0.4	3	1.7	28	11
168	0.1	0.2	0.7	2	21	8
AUC (h·µg/mL)	*99*	*163*	*1 003*	*5 113*	*13 613*	*18 588*

AUC: area under the plasma concentration–time curve; bw: body weight; equiv: equivalents; ROHD: repeated oral high dose; ROLD: repeated oral low dose; SOHD: single oral high dose; SOLD: single oral low dose
Source: Hawkins et al. (1986)

(b) Dermal irritation

Quinclorac (batch no. 83/117; purity not stated) produced no erythema or oedema of the skin when tested in Vienna White rabbits (Grundler & Kirsch, 1983c). Similar results were reported in a more recent study (batch no. COD-000475; purity 99.4%) in New Zealand White rabbits (Gamer & Leibold, 2005c).

(c) Ocular irritation

Quinclorac (batch no. 83/117; purity not stated) produced transient, mild conjunctival effects (scores 0–2) when tested in Vienna White rabbits (Grundler & Kirsch, 1983d). Similar results were reported in a more recent study (batch no. COD-000475; purity 99.4%) in New Zealand White rabbits (Remmele & Leibold, 2005).

Table 4. Tissue distribution of radiolabel in rats administered ^{14}C-labelled quinclorac at 15 mg/kg bw per day for 7 days

	Tissue level of radioactivity 0.5 h after the last dose (µg equiv/g)	
Tissue	**Males**	**Females**
Adrenals	4.3	6.7
Bone marrow	3.4	6.8
Brain	0.7	1.3
Kidney	24	42
Liver	6.3	9.1
Pancreas	4.8	6.5
Plasma	35	62
Thyroid	6.7	11
Whole blood	17	23

bw: body weight; equiv: equivalents
Source: Hawkins et al. (1986)

Table 5. Summary of acute toxicity studies with quinclorac

Species	Strain	Sex	Route	Purity (%)	LD_{50}/LC_{50}	Reference
Rat	Wistar	M & F	Oral gavage	Not stated	2 680 mg/kg bw	Grundler & Kirsch (1983a)
Rat	Wistar	F	Oral gavage	99.4	> 2 000 mg/kg bw	Gamer & Leibold (2005a)
Rat	Wistar	M & F	Dermal	Not stated	> 2 000 mg/kg bw	Grundler & Kirsch (1983b)
Rat	Wistar	M & F	Dermal	99.4	> 2 000 mg/kg bw	Gamer & Leibold (2005b)
Rat	Tif:RAIf	M & F	Inhalation (aerosol[a])	50 (formulated product)	> 5.15 mg/L	Klimisch (1986)

bw: body weight; F: female; LC_{50}: median lethal concentration; LD_{50}: median lethal dose; M: male
[a] Mass median aerodynamic diameter 3.15 µm.

(d) Dermal sensitization

Quinclorac (batch no. COD-000475; purity 99.4%) produced no reactions in a guinea-pig maximization test with a challenge concentration of 25% weight per weight (w/w) (Gamer & Leibold, 2005d). A positive result was reported in an earlier maximization study using quinclorac of a lower purity (batch no. N55; purity 97.4%) and a 25% challenge concentration (Kieczka, 1986).

2.2 Short-term studies of toxicity

(a) Oral administration

Mice

Groups of 10 male and 10 female B6C3F1/CrlBR mice were given diets containing quinclorac (batch no. N57 III/2; purity 98.3%) at 0, 4000, 8000 or 16 000 ppm for 3 months.

Achieved test article intakes were 0, 1001, 1992 and 4555 mg/kg bw per day for males and 0, 1466, 2735 and 5953 mg/kg bw per day for females, respectively. Clinical signs, body weight development, and feed and water consumption were monitored regularly. Samples for clinical chemistry and haematology investigations were taken prior to sacrifice. All animals were subjected to gross pathological examination followed by a microscopic examination. Control and top-dose animals received a full microscopic examination; for the low- and intermediate-dose groups, only lungs, liver, kidneys and gross lesions were examined.

There were no deaths or clinical signs associated with quinclorac administration. Body weights were significantly reduced in all treated groups, but the magnitude at the middle and low dose levels was less than 10% (Table 6). Water consumption was increased consistently at the top dose level, with an increase in blood urea levels in males at the middle and top doses. There was a reduction in relative kidney weights in top-dose males, but there was no associated pathology. Monocyte and eosinophil counts were reduced in a dose-related manner in males, but without statistical significance (Table 6). The pattern of lesions reported at microscopic examination was similar in test and control animals.

Table 6. Findings (means) in the 3-month study in mice receiving quinclorac in the diet

	Males				Females			
Parameter	**0 ppm**	**4 000 ppm**	**8 000 ppm**	**16 000 ppm**	**0 ppm**	**4 000 ppm**	**8 000 ppm**	**16 000 ppm**
Body weight (g)								
Day 0	22.6	22.6	22.4	22.4	19.1	19.1	19.2	18.9
Day 7	23.9	23.9	23.4	22.8*	20.1	19.8	19.9	19.0**
Day 84	29.0	28.3	27.0*	27.0*	26.2	24.8**	24.2**	23.4**
Day 91	31.1	29.6	26.7**	28.0**	26.6	25.2*	24.9**	24.4**
% body weight deficit (day 91)	–	−5%	−8%	−10%	–	−5%	−6%	−8%
Water consumption (g/animal per day)								
Day 7	6.9	6.8	6.9	7.1	5.8	5.9	6.0	6.6
Day 49	5.0	5.0	5.6	6.0	5.2	5.0	5.6	6.1
Day 84	5.0	5.3	5.5	6.7	5.5	5.2	5.9	6.1
Day 91	5.7	5.8	6.5	7.1	5.3	5.7	6.2	6.7
Urea (mmol/L)	8.28	8.98	9.19*	9.25*	7.52	8.16	8.07	8.36
Monocyte (%)	3.90	3.00	2.10	0.20	1.30	0.70	1.40	1.10
Eosinophils (%)	2.00	0.90	0.80	0.50	1.60	0.80	1.00	1.20
Mean cell volume (fL)	43.50	42.70**	42.54**	42.41**	43.34	42.92	42.84	42.85

ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$
Source: Kuehborth et al. (1988)

The no-observed-adverse-effect level (NOAEL) was 4000 ppm (equal to 1001 mg/kg bw per day), based on increased water consumption and blood urea levels in males at 8000 ppm (equal to 1992 mg/kg bw per day). The effects on body weight and mean cell volume at 4000 ppm are small in magnitude and not considered to be adverse (Kuehborth et al., 1988).

A second 3-month mouse study was performed using a single dietary level of quinclorac. Groups of 10 male and 10 female B6C3F1/CrlBR mice were given diets containing quinclorac (batch no. N57 III/2; purity 98.3%) at 0 or 500 ppm for 3 months. Achieved test article intakes were 0 and 85 mg/kg bw per day for males and 0 and 130 mg/kg bw per day for females, respectively. Clinical signs, body weight development, and feed and water consumption were monitored regularly. Samples for clinical chemistry and haematology investigations were taken prior to sacrifice. All animals were subject to gross pathological examination; there was no microscopic examination.

There were no deaths, clinical signs or clinical chemistry findings associated with treatment. Body weight was lower (6%) in females at day 98 only, but this appeared to be associated with a large increase in control values between days 90 and 98 (Table 7). Eosinophil and monocyte counts were reduced, but the reductions showed large intra-animal variation and were not statistically significant. Relative kidney weight was increased in females, but the magnitude was small (< 10%). None of the findings is considered to be adverse.

Table 7. Body and kidney weights (means) in mice receiving quinclorac in the diet for 90 days

	Males		**Females**	
	0 ppm (control)	**500 ppm**	**0 ppm (control)**	**500 ppm**
Body weight (g)				
Day 0	23.2	23.3	19.5	19.4
Day 90	–	–	25.2	24.7
Day 98	33.2	33.0	27.1	25.5*
Relative organ weights (group mean, g)				
Kidneys	1.644	1.584	1.495	1.605**

ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$
Source: Schilling et al. (1988a)

The NOAEL was 500 ppm (equal to 85 mg/kg bw per day), the highest dose tested (Schilling et al., 1988a).

Rats

Groups of 10 male and 10 female Wistar (Chbb=Thom) rats were given diets containing quinclorac (batch no. N32; purity 96.5%) at a dose of 0, 1000, 4000 or 12 000 ppm for 3 months. Achieved test article intakes were 0, 77, 302 and 930 mg/kg bw per day for males and 0, 87, 358 and 1035 mg/kg bw per day for females, respectively. Clinical signs, body weight, and feed and water consumption were monitored regularly. Samples for clinical chemistry and haematology were taken on day 86. Urine analysis samples were obtained on day 80. Ophthalmoscopy was performed on animals in the control and top-dose groups, pretest and prior to sacrifice. All animals were subjected to a gross pathological examination followed by a microscopic examination. Control and top-dose animals received a full microscopic examination; for the low- and intermediate-dose groups, only lungs, liver, kidneys and gross lesions were examined.

An initial deficit in body weight in top-dose males was associated with reduced feed consumption and, although statistically significant, was less than 10% (Table 8). A number of clinical chemistry parameters and water consumption were altered in top-dose animals (Table 8), indicative of potential liver and kidney toxicity. Erythrocyte parameters were reduced in top-dose females. The only pathological findings of note were chronic interstitial nephritis and focal urothelial hyperplasia in top-dose males (Table 8). There were no treatment-related adverse effects in the animals of the low-

Table 8. Findings (means) in rats receiving quinclorac in the diet for 90 days

	Males				Females			
	0 ppm	**1 000 ppm**	**4 000 ppm**	**12 000 ppm**	**0 ppm**	**1 000 ppm**	**4 000 ppm**	**12 000 ppm**
Body weight (g)								
Day 0	160.1	160.6	161.0	159.8	126.3	125.9	126.3	125.6
Day 7	206.6	210.2	209.8	193.0*	149.8	150.9	148.8	142.9
Day 14	256.5	262.5	258.7	240.9*	171.9	172.7	166.0	162.4
Day 49	391.5	400.8	399.7	357.7*	225.6	226.7	221.1	210.2
Day 91	458.8	477.2	477.2	430.9	252.5	259.7	247.7	235.4
Food consumption (g/animal per day)								
Day 7	23.1	23.8	22.9	19.7	17.2	17.5	17.3	15.6
Day 14	25.8	26.9	26.0	24.2	17.4	17.7	17.3	16.5
Day 49	27.4	26.9	26.7	25.5	18.0	18.2	18.8	17.1
Day 91	25.4	25.9	25.4	23.5	17.4	18.1	17.9	16.1
Water consumption (g/day)								
Days 15–16	27.20	27.30	27.40	36.33	18.60	15.90	15.22	19.50
Days 56–57	31.20	25.80	28.90	37.38	21.44	20.70	21.60	24.00
Days 87–88	27.30	29.30	29.70	34.30	23.80	21.90	24.60	32.00
Clinical chemistry								
Bilirubin (µmol/L)	1.842	0.965*	0.608**	0.572**	1.558	1.258	1.359	0.993*
Triglycerides (mmol/L)	2.690	3.434	3.618	2.013*	1.576	2.637*	1.621	1.397
Urea (mmol/L)	7.306	7.278	7.175	7.064	6.976	7.893*	7.029	7.394
ALAT (µkat/L)	0.832	0.883	0.937	1.050*	0.900	0.864	0.846	0.791
ASAT (µkat/L)	1.488	1.939*	2.092	2.599*	2.034	1.677	2.351	1.890
Haematology								
Haemoglobin (mmol/L)	9.246	8.922	9.034	9.036	9.294	9.217	9.200	8.449*
Haematocrit (L/L)	0.411	0.407	0.400	0.390*	0.405	0.402	0.395	0.374*
HBE (fmol)	1.124	1.129	1.107	1.109	1.140	1.135	1.134	1.109**
POLY (%)	9.10	9.90	9.70	11.90	10.90	16.50	13.90	19.80
Lymphocytes (%)	83.30	84.40	82.90	81.40	81.10	74.80	77.20	68.80
Monocytes (%)	5.30	4.50	6.20	5.20	5.70	6.80	7.40	9.50
Histopathology (no. of animals affected/10)								
Chronic interstitial nephritis	0	1	0	4	0	1	0	1
Focal urothelial hyperplasia	0	0	0	2	0	0	0	0
Liver, focal fatty infiltration	0	0	0	1	0	1	1	1

ALAT: alanine aminotransferase: ASAT: aspartate aminotransferase; HBE: haemoglobin per erythrocyte; POLY: neutrophilic segmented granulocytes; ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$
Source: Kuehborth, Deckardt & Hildebrand (1986)

and mid-dose groups. Plasma bilirubin was decreased dose relatedly in all male groups (Table 8), but this is not considered to be adverse in isolation.

The NOAEL was 4000 ppm (equal to 302 mg/kg bw per day), based on a range of clinical chemistry and haematological changes in both sexes and interstitial nephritis and urothelial hyperplasia in males at 12 000 ppm (equal to 930 mg/kg bw per day) (Kuehborth, Deckardt & Hildebrand, 1986).

Dogs

Quinclorac (batch no. N15; purity 93.6%) was offered to groups of Beagle dogs (two of each sex) in the diet at a dose of 0, 1000, 3000, 9000 or 27 000 ppm for 28 days. Achieved intakes of quinclorac were 0, 31, 95, 278 and 912 mg/kg bw per day for males and 0, 36, 108, 315 and 956 mg/kg bw per day for females, respectively. The animals were observed each day for any evident signs of toxicity. Body weights and feed consumption were determined weekly. Blood samples were taken from all animals pretest and on day 25 for examination of haematology and clinical chemistry parameters. Urine samples were taken pretest and on day 22. At the end of the treatment period, all animals were sacrificed and subjected to gross and limited histopathological examination (six organs plus any gross lesions).

At 27 000 ppm, feed consumption was reduced in females, and there was body weight loss over the duration of the study in both sexes. Kidney lesions were present at the top dose level (Table 9). Plasma alkaline phosphatase activity was reduced significantly at 9000 and 27 000 ppm, but this finding is not considered to be adverse in isolation (Table 9).

Table 9. Findings in dogs fed quinclorac in the diet for 28 days

	Males					**Females**				
	0 ppm	**1 000 ppm**	**3 000 ppm**	**9 000 ppm**	**27 000 ppm**	**0 ppm**	**1 000 ppm**	**3 000 ppm**	**9 000 ppm**	**27 000 ppm**
Body weight (mean), kg										
Day 0	10.95	11.45	11.05	11.40	10.60	8.90	9.85	9.75	10.05	9.45
Day 7	10.95	11.40	10.90	11.35	10.05	8.85	9.75	9.65	9.95	8.85
Day 28	11.20	11.65	11.15	11.35	9.75	8.90	9.85	9.70	10.05	8.25
Parameter										
Alkaline phosphatase (day 25 means), µkat/L	5.05	3.72	4.13	2.58	2.19	3.86	2.33	2.87	2.38	1.41
Kidney tubules dilated	0	0	0	0	1	0	0	0	0	2
Kidney interstitial nephritis	0	0	0	0	1	0	0	0	0	2

ppm: parts per million
Source: Hellwig et al. (1985)

The NOAEL was 9000 ppm (equal to 278 mg/kg bw per day), based on body weight loss and kidney lesions at 27 000 ppm (equal to 912 mg/kg bw per day) (Hellwig et al., 1985).

In a 12-month dog study (six of each sex per group), dose levels of quinclorac (batch no. N32, purity 96.5%; and batch no. N55, purity 97.4%) were 0, 1000, 4000 and 12 000 ppm (equal to 0, 35, 139 and 490 mg/kg bw per day for males and 0, 35, 141 and 472 mg/kg bw per day for females, respectively). Clinical signs, body weight development, and feed and water consumption were monitored regularly. Ophthalmoscopic examinations and clinical pathology investigations (haematology, biochemistry and urine analysis) were completed once before and 3 times during the administration period. At the end of the treatment period, all animals were subjected to gross pathological examination followed by an extensive microscopic examination.

Top-dose animals suffered body weight loss at the start of the study, with no subsequent recovery (Table 10); body weights in other treated groups were lower than control values, but within normal variation for Beagle dogs. Feed efficiency was reduced at the top dose. A range of clinical chemistry changes was seen in top-dose animals; some of these, including reductions in creatinine, urea, calcium and bilirubin levels and alkaline phosphatase activity, were also observed at lower dose levels (Table 10). Haemoglobin, mean cell volume and erythrocyte counts were consistently lower in the top-dose group; changes at lower dose levels were mainly sporadic. Increases in relative brain, adrenal and thyroid weights appear to be secondary to the body weight deficits at the top dose level. Kidney and liver weights were increased in absolute and relative terms (Table 10). The increased relative liver weights at the low and middle doses did not exhibit a dose–response relationship and are not considered to be adverse. The increased relative kidney weights in males at 4000 ppm were without any related functional or histopathological changes, but the magnitude (20%) is such that there could be associated adverse effects. The only organs exhibiting treatment-related effects during histopathological examination were liver and kidneys in top-dose animals (Table 10).

The NOAEL was 1000 ppm (equal to 35 mg/kg bw per day), on the basis of increased relative kidney weights (~20%) in males at 4000 ppm (equal to 139 mg/kg bw per day). The changes in clinical chemistry findings at the low dose level are not considered to be adverse (Hellwig et al., 1988a).

(b) Dermal application

Quinclorac (batch no. III/2 N 57; purity 98.29%) was applied to the shaved skin of groups of New Zealand White rabbits at 40 or 200 mg/kg bw per day (five of each sex) or 0 or 1000 mg/kg bw per day (10 of each sex) for 6 hours/day, 7 days/week, for 21 applications. Animals were observed for clinical signs, local irritation, and feed consumption and body weight changes. Ophthalmoscopy and blood sampling were performed during week 3. At necropsy, a range of tissues was examined, and a limited number of organs were weighed and examined microscopically.

There were no deaths or clinical signs of toxicity. Animals of the high-dose group showed partly yellowish discoloured skin, which was attributed to the colour of the applied test material. A significant increase in absolute kidney weight in top-dose males was related to the higher body weight in this group. A dose-related reduction in uric acid was seen in males, but is not considered adverse. No other treatment-related effects were noted during the entire study period.

The NOAEL was 1000 mg/kg bw per day, the highest dose tested (Ullmann et al., 1990).

(c) Exposure by inhalation

No data were submitted. Quinclorac has a low vapour pressure ($< 10^{-8}$ Pa), and respirable exposures are expected to be very low.

2.3 Long-term studies of toxicity and carcinogenicity

Mice

Groups of mice (B6C3F1/CrlBr), 50 of each sex per dose level, received quinclorac (batch no. N55, purity 97.4%; and batch no. N57, purity 98.3%) at a dietary level of 0, 1000, 4000 or 8000 ppm for 78 weeks. The average compound intakes were 0, 170, 711 and 1444 mg/kg bw per day for males

Table 10. Findings in dogs fed quinclorac in the diet for 12 months

	Males				Females			
	0 ppm	**1 000 ppm**	**4 000 ppm**	**12 000 ppm**	**0 ppm**	**1 000 ppm**	**4 000 ppm**	**12 000 ppm**
Body weight (group mean values, kg)								
Day 0	8.8	8.7	8.7	8.6	9.0	9.0	8.8	8.9
Day 70	10.3	9.5	9.4	8.2*	9.8	9.7	9.6	8.5
Day 91	10.5	9.6	9.8	8.5**	10.1	10.0	9.9	8.7
Day 182	11.3	10.7	10.8	9.0**	10.8	10.5	10.7	9.3
Day 273	11.3	10.6	10.4	8.7**	10.8	10.5	10.5	9.0
Day 364	11.2	10.4	10.0	8.3**	10.9	10.4	10.3	9.1
Feed efficiency (group means)								
Weeks 1–52	1.9	1.3	1.0	−0.3	1.2	1.1	1.2	−0.1
Creatinine (group means, µmol/L)								
Pre-dosing	76.0	75.7	71.7	70.3	83.8	72.2	78. 8	79.4
13 weeks	86.4*	80.0	77.8*	66.4**	84.1	85.4*	81.2	71.6**
26 weeks	86.3	80.7	75.4	58.6**	86.4	79.1*	78.0*	65.8**
52 weeks	86.2	78.3	69.7**	53.1**	85.5	80.3	74.6*	61.4**
Urea (group means, mmol/L)								
Pre-dosing	4.16	4.58	3.99	4.12	5.25	4.30	4.42	4.43
52 weeks	8.45*	4.49	4.35*	4.24*	5.55*	5.36	3.73**	4.19*
Calcium (group means, mmol/L)								
Pre-dosing	2.88	2.87	2.86	2.77	2.86	2.87	2.85	2.82
13 weeks	2.82	2.75*	2.75	2.66*	2.80	2.70**	2.73*	2.68**
26 weeks	2.77	2.72*	2.73	2.61*	2.76*	2.78	2.71*	2.64**
52 weeks	2.64**	2.61**	2.55**	2.49**	2.80	2.79	2.71**	2.66**
Total bilirubin (group means, µmol/L)								
Pre-dosing	2.63	2.70	2.27	3.12	3.29	2.98	3.17	2.93
13 weeks	3.55	3.74*	2.09*	2.40	3.46	3.59	3.14	2.44
26 weeks	2.49	2.71	1.72	1.22**	2.22	2.39	1.95	1.21**
52 weeks	2.81	2.29	1.25*	1.18*	2.44	2.42	2.30	1.48**
Alkaline phosphatase (group means, µkat/L)								

	Males				Females			
	0 ppm	**1 000 ppm**	**4 000 ppm**	**12 000 ppm**	**0 ppm**	**1 000 ppm**	**4 000 ppm**	**12 000 ppm**
Pre-dosing	6.42	6.05	5.31	4.90*	4.37	5.91	6.19*	5.37
13 weeks	4.88	4.57	2.82**	2.36**	3.34	4.17*	3.06**	2.20**
26 weeks	3.71*	2.99**	2.13**	2.28**	2.92*	4.32	3.18**	2.31**
52 weeks	4.23	3.93	2.28**	3.04*	3.51	4.89	3.90*	3.18*
Haemoglobin (group means, mmol/L)								
Pre-dosing	8.80	9.01	8.95	8.31	9.21	8.57*	9.23	8.73
13 weeks	9.67	9.33	9.16	7.41**	9.79	9.40	10.1*	8.52*
26 weeks	10.1	10.0	10.0	8.25**	10.5	9.77*	9.49*	8.73**
52 weeks	10.4	10.2	9.97	8.63**	10.2	9.79	10.3	8.74*
Erythrocytes (group means, 10^{12}/L)								
Pre-dosing	6.16	6.30	6.20	5.83	6.42	6.00	6.50	6.13
13 weeks	6.60	6.30	6.29	8.28**	6.62	6.38	6.88	6.11
26 weeks	6.79	6.75	6.83	5.82**	7.10**	6.64	6.47*	6.22**
52 weeks	6.96	6.89*	6.81	6.04**	6.83	6.65	6.93	6.22
MCV (group means, fL)								
Pre-dosing	69.8	69.6	69.7	69.1	71.4	71.0	70.7	71.2
13 weeks	69.7	69.8	69.3	67.3**	70.2	70.2	69.5	67.1**
26 weeks	70.5	70.4	69.6	67.9**	71.5	70.5	70.0	67.1**
52 weeks	70.9	70.7	69.9	68.8	71.6	70.2	70.9	68.0**
Organ weights (group mean values)								
Liver (absolute; g)	365.3	383.3	350.2	406.1	360.0	411.9	402.7	472.7**
Liver (relative; % body wt)	3.258	3.692	3.522	4.902**	3.319	3.987*	3.964*	5.220**
Kidney (absolute; g)	52.3	51.6	56.5	60.1	52.5	54.2	55.6	60.3
Kidneys (relative; % body wt)	0.469	0.499	0.563**	0.726**	0.485	0.527	0.548	0.666**
Brain (relative; % body wt)	0.723	0.762	0.810	1.028**	0.695	0.755	0.758	0.820*
Adrenal (relative; % body wt)	0.009 7	0.010 3	0.011 6	0.013 5**	0.011 6	0.014 8	0.014 8	0.014 8

	Males				Females			
	0 ppm	**1 000 ppm**	**4 000 ppm**	**12 000 ppm**	**0 ppm**	**1 000 ppm**	**4 000 ppm**	**12 000 ppm**
Thyroid (relative; % body wt)	0.007 4	0.008 2	0.008 4	0.010 3*	0.007 8	0.009 7	0.008 5	0.012 3**
Histopathology findings								
Liver congestion	0	0	0	1	0	0	0	0
Liver single-cell necrosis	0	0	0	2	0	0	0	2
Kidney hydropic degeneration	0	0	0	2	0	0	0	2

MCV: mean cell volume; ppm: parts per million; wt: weight; *: $P < 0.05$; **: $P < 0.01$
Source: Hellwig et al. (1988a)

and 0, 213, 869 and 1828 mg/kg bw per day for females, respectively. Blood samples were taken during week 78 from 10 animals of each sex per group for evaluation of haematological parameters. All animals received a gross examination. An extensive microscopic examination was performed on all control and top-dose animals, with only gross lesions, lung, liver, kidney and gallbladder examined in the mid- and low-dose groups.

There were no effects on mortality, appearance or behaviour. Survival at week 78 was greater than 90% in all groups. The only notable finding was a progressive and dose-related reduction in body weight in all groups exposed to quinclorac (Table 11). The body weight deficit in males from the 1000 ppm group was less than 10% and is not considered to be adverse in isolation. There were no effects on haematological parameters and no increases in non-neoplastic or neoplastic lesions.

Table 11. Body weights of mice receiving quinclorac in the diet for 78 weeks

	Mean body weight (g)							
	Males				Females			
Day	**0 ppm**	**1 000 ppm**	**4 000 ppm**	**8 000 ppm**	**0 ppm**	**1 000 ppm**	**4 000 ppm**	**8 000 ppm**
0	21.3	21.2	21.1	21.0	17.7	17.5	17.4	17.4
7	22.2	22.0	21.4**	21.3**	18.7	18.2*	17.9**	17.8**
182	32.0	31.9	29.4**	28.8**	28.6	27.6	26.9**	26.2**
350	35.4	34.0*	31.5**	30.1**	34.8	31.0**	30.1**	28.9**
546	34.0	31.3**	29.4**	28.6**	33.6	28.8**	28.5**	27.6**

ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$
Source: Schilling et al. (1988c)

No NOAEL for non-neoplastic toxicity could be identified. The lowest-observed-adverse-effect level (LOAEL) for non-neoplastic toxicity was 1000 ppm (equal to 213 mg/kg bw per day), based on significantly reduced body weight (> 10%) in females at all doses. The NOAEL for carcinogenicity was 8000 ppm (equal to 1444 mg/kg bw per day), the highest dose tested (Schilling et al., 1988c).

A supplementary 78-week study in mice was performed to determine a NOAEL for quinclorac in a chronic mouse study. Groups of mice (B6C3F1/CrlBr), 50 of each sex per group, received quinclorac (batch no. N57; purity 98.3%) at a dietary level of 0 or 250 ppm for 78 weeks. Achieved quinclorac intakes in the main groups were 0 and 42 mg/kg bw per day for males and 0 and 52 mg/kg bw per day for females, respectively. A satellite group of 10 mice of each sex was sacrificed after 26 weeks. Blood samples were taken during week 26 from the satellite group and week 78 from 10 animals of each sex per group for evaluation of haematological parameters. All main group animals received an extensive gross examination; no histopathological examinations were performed.

There were no effects on clinical signs or mortality. Survival was 90% or higher in all groups. Feed consumption was consistently lower in both sexes of treated mice during the first 6 months of the study and in females for the majority of the study. Body weights were similar in treated and control mice. There were no effects on haematology, organ weights or gross pathological findings.

The NOAEL was 250 ppm (equal to 52 mg/kg bw per day in females), the only dose tested (Schilling et al., 1988d).

Rats

Groups of 50 male and 50 female Wistar (Chbb=Thom) rats were given diets containing quinclorac (batch no. N55, purity 97.4%; and batch no. N57, purity 98.3%) at a dietary level of 0, 1000, 4000 or 8000 ppm for 2 years for evaluation of carcinogenic potential. Satellite groups received diets containing quinclorac at 0, 1000, 4000, 8000 or 12 000 ppm for evaluation of chronic toxicity over 2 years (20 rats of each sex per group) or 12 months (10 rats of each sex per group). Achieved intakes were 0, 55, 221 and 444 mg/kg bw per day for males and 0, 66, 262 and 529 mg/kg bw per day for females, respectively, in the carcinogenicity phase. In the satellite groups, mean test article intakes were reported as 0, 55, 221, 444 and 675 mg/kg bw per day for males and 0, 66, 262, 529 and 832 mg/kg bw per day per day for females, respectively.

Regular investigations of mortality, clinical signs, feed and water consumption, and body weight were performed. Ophthalmoscopy was performed on control and 12 000 ppm animals pretest and at 12 and 24 months. Blood samples for clinical chemistry and haematology were taken from satellite groups at 3, 6, 12, 18 and 24 months. All animals received a gross examination. A wide range of tissues from animals in the control and top-dose groups was examined histopathologically; liver, kidney, lung and gross lesions from low- and intermediate-dose group animals were also examined histopathologically. A supplementary investigation (Schilling, Maita & Hildebrand, 1991; Tobia & Mascianica, 1991) evaluated the pancreas from all animals in the main and satellite groups.

Survival was unaffected by quinclorac treatment and was greater than 65% in all carcinogenicity groups. Water consumption was routinely higher (~20%) in all groups receiving 8000 and 12 000 ppm, but the increase did not achieve statistical significance. Body weights were lower (~10%) in females in the 12 000 ppm group, attaining statistical significance between days 518 and 658 in the main group. The patterns of clinical signs, haematology results, clinical chemistry findings, and urine analysis results were similar in test and control groups. Relative kidney weights were increased by more than 10% in the 24-month satellite group, in males at 4000 ppm and above and in females at 8000 ppm; this was not reproduced in the main group, and statistical significance was not achieved (Table 12). The only renal lesion demonstrating a relationship to quinclorac was renal pelvis mineralization, which was increased in the main groups but not in the 24-month satellite groups. Overall, it is concluded that the renal findings do not present a coherent relationship to treatment and are not an adverse effect of quinclorac administration.

An increase in splenic haemangiosarcoma in top-dose males was not repeated in females and was not associated with any preneoplastic changes, but it was associated with an absence of haemangioma of the spleen; this is not considered to be an indication of a carcinogenic response to quinclorac. An increase in pancreatic acinar cell tumours (Table 12) was seen in top-dose males of the main and 24-month satellite groups, but this was not repeated in females; the incidence of hyperplasia was higher than the control incidence, but exhibited no dose–response relationship. Historical control

Table 12. Findings in the 24-month study of quinclorac in rats

Parameter	0 ppm	1 000 ppm	4 000 ppm	8 000 ppm	12 000 ppm
Males					
Body weight (g)					
12 months (satellite)	646	629	642	683	656
24 months (main)	679	694	715	702	–
24 months (satellite)	715	721	693	703	673
Main group (n = 50 rats)					
Total number of neoplasms	88	73	63	83	–
Spleen, haemangioma	2	0	1	0	–
Spleen, haemangiosarcoma	0	0	0	2	–
Pancreas, acinar cell adenoma	0	1	0	3	–
Pancreas, acinar cell adenocarcinoma	0	0	0	1	–
Pancreas, acinar cell hyperplasia	3	5	8	6	–
Pancreas, islet cell adenoma	1	1	1	0	–
Mineralization of renal pelvis					
Main	18	20	17	27	–
24-month satellite	5	8	11	10	5
Relative kidney weight (% of body weight)					
Main	0.61	0.63	0.59	0.62	–
24-month satellite	0.58	0.58	0.66	0.66	0.66
12-month satellite	0.54	0.55	0.54	0.53	0.55
Females					
Body weight (g)					
12 months (satellite)	374	350	354	344	335
24 months (main)	425	413	414	395	–
24 months (satellite)	401	394	401	397	366
Main group (n = 50 rats)					
Total number of neoplasms	86	90	84	79	–
Spleen, haemangiosarcoma	0	0	0	1	–
Pancreas, acinar cell adenoma	0	0	0	0	–
Pancreas, acinar cell adenocarcinoma	0	0	0	0	–
Pancreas, acinar cell hyperplasia	1	0	1	3	–
Pancreas, islet cell adenoma	0	0	0	1	–
Mineralization of renal pelvis					
Main	14	15	14	22	–
Satellite	2	2	2	4	3
Relative kidney weight (% of body weight)					
Main	0.71	0.72	0.78	0.76	–

Parameter	0 ppm	1 000 ppm	4 000 ppm	8 000 ppm	12 000 ppm
24-month satellite	0.77	0.80	0.80	0.85	0.84
12-month satellite	0.63	0.64	0.65	0.67	0.66

ppm: parts per million
Source: Schilling et al. (1988b)

data were supplied (see Tables A1 and A2 in Appendix 1): the mean incidence of acinar cell adenoma in males was 4.4% (range 0–18%); for adenocarcinoma, the mean incidence was 0.7% (range 0–5.1%). As the incidence of pancreatic tumours is within the pattern of the contemporary historical control data for the test facility, quinclorac is considered not to have carcinogenic potential in rats.

The NOAEL for general toxicity was 8000 ppm (equal to 529 mg/kg bw per day), based on lower body weights (~10%) in females at 12 000 ppm (equal to 832 mg/kg bw per day).

The NOAEL for carcinogenicity was 8000 ppm (equal to 444 mg/kg bw per day), the highest dose tested in the carcinogenicity segment (Schilling et al., 1988b).

2.4 Genotoxicity

(a) In vitro studies

Quinclorac was tested for genotoxicity in an adequate range of assays. Quinclorac was not genotoxic in an Ames test with batch no. N55, but a positive result was seen with batch no. N15, which was reported to contain impurities with genotoxic potential. Supplemental gene mutation assays with *Escherichia coli* were negative. Negative results were seen in a rec assay in *Bacillus subtilis.* Positive results were produced in a cytogenicity assay in human lymphocytes at high concentrations (see Table A3 in Appendix 1). Inconsistent results were seen in a gene mutation assay in Chinese hamster ovary cells; negative results were seen in the first assay, but a positive result was seen in the second assay in the presence of metabolic activation (see Table A4 in Appendix 4; see also Table 13).

(b) In vivo studies

Quinclorac was not genotoxic in assays for micronucleus induction in mouse bone marrow and unscheduled DNA synthesis in rat liver (Table 13).

2.5 Reproductive and developmental toxicity

(a) Multigeneration studies

Groups of Wistar (Chbb=Thom (SPF)) rats (24 of each sex per group) received diets containing quinclorac (batch no. N55 III, purity 97.38%; and batch no. N57 III/2, purity 98.29%) at 0, 1000, 4000 or 12 000 ppm. Achieved intakes were reported to be approximately 0, 96, 381 and 1180 mg/kg bw per day at 0, 1000, 4000 and 12 000 ppm, respectively. There were two litters in the first generation and one in the second. Parents were mated 1:1 after approximately 10 weeks of exposure to quinclorac for the F_{1a} and F_{2a} litters. For the F_{1b} mating, parents were paired 10 days after weaning of the F_{1a} pups. Litters were not culled on day 4 postpartum. Clinical signs, body weights, feed consumption, mating parameters, gestation and delivery parameters, pup survival, and physical and behavioural development (ear and eye opening, grip strength and pupillary reflex) were recorded. No evaluation of date of sexual maturation was included in the protocol. A gross necropsy examination was performed on all pups not selected for mating. Further examinations were performed on any pups found dead or dying or showing macroscopic changes. All parental animals were necropsied after weaning of their offspring and subjected to pathological examination.

Table 13. Genotoxicity studies with quinclorac

Test	Target	Concentration or dose tested	Purity (%)	Results	Reference
In vitro					
Gene mutations in bacteria	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA 1537	20–5 000 µg/plate (±S9)	Purity not stated (batch no. N55)	Negative ±S9	Gelbke & Engelhardt (1985)
Gene mutations in bacteria	*Escherichia coli* WP2uvrA	20–5 000 µg/plate (±S9)	Purity not stated (batch no. N55)	Negative ±S9	Gelbke & Engelhardt (1986c)
Gene mutations in bacteria	*S. typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. coli* WP2uvrA	20–5 000 µg/plate (±S9)	98.3	Negative ±S9	Hoffmann & Engelhardt (1988)
Gene mutations in bacteria	*S. typhimurium* strain TA1535	20–5 000 µg/plate (±S9)	Purity not stated (batch no. N15)	Positive ±S9[a]	Gelbke & Engelhardt (1985)
Gene mutations in bacteria	*Bacillus subtilis* H17 and M45 (rec assay)	1–10 000 µg/plate (±S9)	Purity not stated (batch no. N57)	Negative ±S9	Hoorn (1987)
Gene mutations in mammalian cells	Chinese hamster ovary cells (HPRT)	46, 100, 215, 464, 1 000 and 2 150 µg/mL (±S9)	97.4	Equivocal +S9 Negative –S9	Jaeckh & Hoffmann (1990)
Chromosomal aberrations	Human lymphocytes	250, 500 and 1 000 µg/mL (±S9)	96.5	Positive ±S9	Gelbke & Engelhardt (1986a)
In vivo					
Micronucleus test	Male and female NMRI mice (bone marrow)	500, 1 000 and 2 000 mg/kg bw	96.5	Negative	Gelbke & Engelhardt (1986b)
Unscheduled DNA synthesis	Male Wistar rats (liver)	100 and 1 000 mg/kg bw	97.4	Negative	Fautz & Voelkner (1991)

bw: body weight; DNA: deoxyribonucleic acid; HPRT: hypoxanthine–guanine phosphoribosyltransferase; S9: 9000 × *g* supernatant fraction from rat liver homogenate

[a] At cytotoxic concentrations.

There was no effect on mating, fertility, pregnancy outcome, litter size or pup survival (Table 14). Significant reductions in maternal body weight gain were seen in males and in females during pregnancy and lactation at 12 000 ppm in the F_1 matings. Pup body weights were similar to control values at birth, but were significantly lower by day 21 at 12 000 ppm in all generations (Table 14). Examinations of pups and parental animals did not identify any adverse effects of quinclorac administration. Attainment of physical developmental markers and behavioural results were similar in all groups of pups. Top-dose female, but not male, parents had an increased incidence of nephritis in both generations, but a reduction in calcification in F_1 parents (Table 15). There were no adverse findings in the reproductive organs.

The NOAEL for reproductive toxicity was 12 000 ppm (equivalent to 1180 mg/kg bw per day), the highest dose tested.

Table 14. Litter size and pup weights in rats exposed to quinclorac in the diet

	0 ppm		1 000 ppm		4 000 ppm		12 000 ppm	
	Day 0	**Day 21**	**Day 0**	**Day 21**	**Day 0**	**Day 21**	**Day 0**	**Day 21**
Pups alive/litter								
F_{1a}	12.4	12.0	12.1	11.5	12.5	12.1	12.4	11.1
F_{1b}	14.0	13.6	13.8	12.9	14.1	13.8	13.1	12.8
F_{2a}	12.5	11.7	13.2	12.4	11.4	11.1	11.7	10.7
Pup weight (g), males								
F_{1a}	6.1	45	6.3	46	6.2	43	5.9	33**
F_{1b}	6.0	43	6.1	45	6.2	41	6.0	35**
F_{2a}	6.1	48	6.0	47	6.2	47	5.7	37**
Pup weight (g), females								
F_{1a}	5.8	43	6.0	44	5.9	41	5.6	32**
F_{1b}	5.7	41	5.9	43	5.8	39	5.8	35**
F_{2a}	5.9	46	5.6	45	5.8	46	5.5*	37**

F_1: first filial generation; F_2: second filial generation; ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$
Source: Hellwig et al. (1988b)

Table 15. Renal pathology findings in female parental rats exposed to quinclorac

Parameter	**0 ppm**	**1 000 ppm**	**4 000 ppm**	**12 000 ppm**
F_0 females				
Interstitial nephritis	4	1	4	16
Calcification (cortex and medulla)	21	21	18	20
F_1 females				
Interstitial nephritis	6	5	4	17
Calcification (cortex and medulla)	23	19	11	1

F_0: parental generation; F_1: first filial generation; ppm: parts per million
Source: Hellwig et al. (1988b)

The NOAEL for parental toxicity was 4000 ppm (equivalent to 381 mg/kg bw per day), based on an increase in the incidence of interstitial nephritis in females at 12 000 ppm (equivalent to 1180 mg/kg bw per day).

The NOAEL for offspring toxicity was 4000 ppm (equivalent to 381 mg/kg bw per day), based on reduced pup weights during lactation at 12 000 ppm (equivalent to 1180 mg/kg bw per day) (Hellwig et al., 1988b).

(b) Developmental toxicity

Rats

Groups of 25 female Wistar rats received quinclorac (batch no. N32; purity 96.5%) by gavage in 0.5% carboxymethyl cellulose in distilled water at a dose of 0, 24.4, 146 or 438 mg/kg bw per day on days 6–15 of gestation. Dams were sacrificed on day 20, and the uterine contents were removed

and examined. Viable fetuses were enumerated and examined for external, visceral and skeletal abnormalities.

In the 438 mg/kg bw per day dose group, two dams died, and another had to be sacrificed during the treatment period. The general state of health of these animals deteriorated during treatment; at necropsy, severe ulcerations of the glandular stomach were evident. In this test group, a significant decrease in feed consumption and a marked increase in water intake were observed during the dosing phase, as well as a slight body weight loss at the beginning of the treatment period (Table 16). The body weight deficit is of a similar magnitude to the reduction in feed consumption. In the 24.4 and 146 mg/kg bw per day dose groups, there were no biologically relevant changes in clinical signs, feed intake, water intake, body weight or macroscopic findings. A statistically significant increase in water consumption (25%) was noted at 146 mg/kg bw per day on days 7–8 of gestation, but not subsequently.

There were no effects on number of viable fetuses or the incidence of fetal abnormalities or variations (Table 17). Fetal weights were slightly higher in treated groups, but this is considered to be of no biological relevance.

The maternal NOAEL was 146 mg/kg bw per day, on the basis of mortality, severe ulcerations of the glandular stomach, reduced feed consumption and increased water consumption at 438 mg/kg bw per day.

The NOAEL for embryo and fetal toxicity was 438 mg/kg bw per day, the highest dose tested (Hellwig, 1987).

Table 16. Feed consumption, water intake and body weight data in a developmental toxicity study of quinclorac in rats

Parameter	0 mg/kg bw per day	24.4 mg/kg bw per day	146 mg/kg bw per day	438 mg/kg bw per day
Feed consumption (g)				
Days 7–8	48	46	49	42**
Days 9–10	50	48	52	43**
Days 11–13	80	76	79	71*
Days 18–20	88	85	88	87
Water intake (g)				
Days 7–8	50	50	63**	83**
Days 9–10	53	51	58	89**
Days 11–13	92	91	95	137**
Days 18–20	369	355	369	417**
Body weight gain (g)				
Days 6–8	7.4	6.2	7.0	−2.6
Days 8–10	11.5	11.6	12.8	8.6
Days 0–20	145	140	150	140
Gravid uterus weight (g)	70	68	77	71

bw: body weight; *: $P < 0.05$; **: $P < 0.01$
Source: Hellwig (1987)

Table 17. Fetal data in a developmental toxicity study of quinclorac in rats

Observation	No. of fetuses / No. of litters affected			
	0 mg/kg bw per day	**24.4 mg/kg bw per day**	**146 mg/kg bw per day**	**438 mg/kg bw per day**
Fetal weight (g)	3.27	3.32*	3.33*	3.29*
No. of fetuses / no. of litters evaluated	321 / 25	297 / 22	307 / 23	259 / 20
Total skeletal anomalies	7 / 4	9 / 9	7 / 6	3 / 3
Total visceral anomalies	1 / 1	1 / 1	1 / 1	3 / 3
Total skeletal variations	33 / 16	24 / 15	38 / 20	23 / 15

bw: body weight; *: $P < 0.05$
Source: Hellwig (1987)

Rabbits

Quinclorac (batch no. N 57 III/2; purity unspecified) was administered to groups of 15 pregnant Himalayan rabbits via gavage in 0.5% carboxymethyl cellulose at a dose level of 0, 70, 200 or 600 mg/kg bw per day on days 7–19 of gestation. On day 29 post-insemination, all animals were sacrificed, and the fetuses were removed by caesarean section. Uterine contents and the fetuses were examined, including soft tissue and skeletal evaluations.

Administration of quinclorac caused severe signs of maternal toxicity at 600 mg/kg bw per day and slight toxicity at 200 mg/kg bw per day. In the 600 mg/kg bw per day dose group, severely reduced feed consumption and reductions in body weight were recorded (Table 18). There were also clinical signs, including reduced or no defecation, diarrhoea, apathy and/or poor general state. Water consumption was similar to that of controls. There were six deaths in the top-dose group between days 14 and 21 of gestation, five of which were considered by the study report authors to be compound related; the remaining one was attributed to dosing error. At necropsy, the findings included a reduction in uterine weights, an increased number of dead implantations/reduced number of live fetuses and slightly reduced fetal weights. An increase in the proportion of fetuses with skeletal variations was not associated with a specific variation (Table 19). In the 200 mg/kg bw per day dose group, slightly reduced feed consumption by the does during the treatment period and a trend towards reduced feed consumption, body weight and body weight gain were observed (Table 18), but the pattern and magnitude were not considered to be biologically relevant. There were no developmental effects at 200 mg/kg bw per day (Table 19). In the 70 mg/kg bw per day dose group, there were no notable effects of quinclorac.

The NOAEL for maternal toxicity was 200 mg/kg bw per day, on the basis of mortality and body weight loss at 600 mg/kg bw per day.

The NOAEL for embryo and fetal toxicity was 200 mg/kg bw per day, based on reduced number of viable fetuses, reduced fetal weight and an increase in fetuses with skeletal variations at 600 mg/kg bw per day (Hellwig, Hildebrand & Shirasu, 1988).

2.6 Special studies

(a) Neurotoxicity

Acute neurotoxicity

Groups of Crl:WI(Han) rats (10 of each sex) received quinclorac (batch no. 479-480; purity 99.9%) at 0, 150, 500 or 1500 mg/kg bw by gavage in 1% carboxymethyl cellulose in water. Animals were subjected to a functional observational battery and assessments of locomotor activity 7 days prior to dosing, at 3–5 hours on the day of dosing and at 7 and 14 days post-dosing. The functional

Table 18. Feed intake and body weight data for does in a developmental toxicity study of quinclorac in rabbits

Parameter	0 mg/kg bw per day	70 mg/kg bw per day	200 mg/kg bw per day	600 mg/kg bw per day
Number of does with viable fetuses	14	13	13	6
Feed consumption (g/animal per day)				
Days 4–7	133	129	127	137
Days 7–9	122	117	100	44
Days 14–16	95	96	90	50
Days 23–25	114	114	113	125
Body weight (kg)				
Day 0	2.29	2.28	2.29	2.28
Day 29	2.63	2.62	2.59	2.49*
Body weight gain (g)				
Days 4–7	7.6	10.8	17.2	23.4
Days 7–9	12	8.6	−2.2	−127**
Days 14–16	28	37	26	−37**
Mean gravid uterine weight (g)	303	293	311	238*

bw: body weight; *: $P < 0.05$; **: $P < 0.01$
Source: Hellwig, Hildebrand & Shirasu (1988)

Table 19. Fetal data from a developmental toxicity study of quinclorac in rabbits

	No. of fetuses / No. of litters affected			
Observation	**0 mg/kg bw per day**	**70 mg/kg bw per day**	**200 mg/kg bw per day**	**600 mg/kg bw per day**
No. of fetuses evaluated / no. of litters evaluated	75 / 13	69 / 13	75 / 13	35 / 6
Mean no. of live fetuses/litter	5.4	5.3	5.8	4.4
Mean pup weight (g)	42	41	40	39*
Total external abnormalities	1 / 1	1 / 1	1 / 1	2 / 1
Total soft tissue malformations	1 / 1	3 / 2	1 / 1	1 / 1
Total soft tissue variations	38 / 11	43 / 12	43 / 12	17 / 5
Total skeletal malformations	0	0	0	1 / 1
Total skeletal variations	9 / 6	13 / 8	7 / 5	11 / 6*
Total skeletal retardations	41 / 12	31 / 12	27 / 8*	23 / 6

bw: body weight; *: $P < 0.05$
Source: Hellwig, Hildebrand & Shirasu (1988)

observational battery included open-field, reflex, neuromuscular and physiological assessments. At sacrifice, half the animals were perfused with 2.5% buffered glutaraldehyde, a full postmortem was performed and samples of a range of nervous tissue and muscle were preserved in formaldehyde, processed and then examined microscopically.

Male rats of the 1500 mg/kg bw dose group showed impaired body weight gain at days 7 (35% deficit) and 14 (15% deficit). Clinical signs and functional observational battery changes were observed on the day of administration at the highest dose level of 1500 mg/kg bw. Motor activity was reduced, with a dose–response relationship for magnitude, on study day 0, 4–5 hours post-dosing, in both sexes of the 1500 mg/kg bw dose group and in males at 500 mg/kg bw. Although a statistically significant decrease was seen in males at 150 mg/kg bw, this group showed a consistently low activity pretest and on days 7 and 14 post-dosing (Table 20). The findings in the low-dose males are considered not to be treatment related. All findings were reversible and not observed on study days 7 and 14. There were no effects noted for neuropathology or brain weight determinations.

Table 20. Locomotor results in rats (10 per group) dosed with quinclorac (total beam breaks in 12 intervals of 5 minutes each)

	Mean number of beam interruptions							
	0 mg/kg bw		**150 mg/kg bw**		**500 mg/kg bw**		**1 500 mg/kg bw**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Day −7, pretest	3 939	3 665	3 028	3 727	3 631	3 753	3 979	3 398
(% control)			(77)	(102)	(92)	(102)	(101)	(93)
Day 0	3 554	3 826	2 622*	4 641	2 425*	3 125	1 807**	2 772*
(% control)			(74)	(121)	(63)	(82)	(51)	(72)
Day 7	3 419	4 793	2 929	5 037	3 340	3 967	3 467	4 012
(% control)			(86)	(105)	(98)	(83)	(101)	(84)
Day 14	3 717	4 563	2 862	6 736	3 751	3 699	3 748	5 129
(% control)			(77)	(148)	(101)	(81)	(101)	(112)

bw: body weight: F: female; M: male; *: $P \leq 0.05$; **: $P \leq 0.01$
Source: Buesen et al. (2012a)

The NOAEL was 150 mg/kg bw, based on reduced motor activity in males at 500 mg/kg bw (Buesen et al., 2012a).

A benchmark dose (BMD) assessment was performed, using the United States Environmental Protection Agency's Benchmark Dose Software (BMDS), a discriminating parameter of 1 standard deviation and a Hill model. Values for the total locomotor activity BMD and lower limit on the benchmark dose (BMDL) for males rats were 106 mg/kg bw and 33 mg/kg bw, respectively (Dammann, 2015).

Subchronic neurotoxicity

Groups of Crl:WI(Han) rats (10 of each sex) received quinclorac (batch no. 479-480; purity 99.9%) at a dietary concentration of 0, 1500, 5000 or 15 000 ppm over a period of 13 weeks. Achieved concentrations, stability and homogeneity were verified by analysis. Achieved test material intakes were 0, 96, 301 and 976 mg/kg bw per day for males and 0, 112, 368 and 1142 mg/kg bw per day for females, respectively. Routine examinations of feed consumption, body weight and clinical signs were performed. Detailed clinical examinations in an open field were conducted prior to the start of the administration period and weekly thereafter. Functional observational batteries and motor activity measurements were carried out on study days −7, 1, 22, 50 and 85. Five animals of each sex per test group were fixed by in situ perfusion and subjected to neuropathological examinations.

Body weight at termination was approximately 5% lower in both sexes at 15 000 ppm; this was not statistically significant and is not considered to be adverse. No mortality occurred during the

study, and no treatment-related clinical signs were observed. Functional observational batteries and motor activity measurements revealed no test material–related neurobehavioural effects at any concentration on study days 1, 22, 50 and 85. There were no effects on neuropathology or brain weight determination.

Under the conditions of this study, the NOAEL for neurotoxicity and general toxicity was 15 000 ppm (equal to 976 mg/kg bw per day), the highest dose tested (Buesen et al., 2012b).

(b) Immunotoxicity

Quinclorac (batch no. 479-480; purity 99.9%) was administered via the diet to groups of eight female C57BL/6J Rj mice at a dose level of 0, 500, 1500 or 5000 ppm over a period of 4 weeks for evaluation of immunotoxicity (sheep red blood cell [sRBC] immunoglobulin M [IgM] antibody titres, spleen and thymus weights and pathology). Quinclorac intakes were 0, 176, 439 and 1760 mg/kg bw per day, respectively. A positive control group received cyclophosphamide monohydrate (10 mg/kg bw per day). Clinical signs, body weight development, and feed and water consumption were monitored.

Clinical examination of the animals treated with the test material revealed no adverse treatment-related findings. There were no effects on the spleen or thymus. sRBC IgM titres were reduced slightly at the top dose level, but mean values were within the typical variation for the parameter (Table 21). The sensitivity of the assay was confirmed by significant findings in the positive control group.

Table 21. SRBC IgM antibody titres in mice receiving quinclorac in the diet for 4 weeks

Parameter	0 ppm	500 ppm	1 500 ppm	5 000 ppm
sRBC mean	3 134	2 884	2 922	2 359
SD	492	356	1 379	600
Range	2 168–3 564	2 263–3 386	493–4 605	1 175–3 070

ppm: parts per million; SD: standard deviation; sRBC: sheep red blood cells
Source: Buesen et al. (2010)

The NOAEL for immunotoxicity was 5000 ppm (equal to 1760 mg/kg bw per day), the highest dose tested (Buesen et al., 2010).

(c) Toxicity of metabolites

Studies of absorption, excretion and metabolism, acute oral toxicity and repeated-dose oral toxicity (90 days) have been performed on quinclorac methyl ester (BAS Reg. No. 161555), a plant metabolite of quinclorac.

Absorption, distribution and excretion

In an initial investigation, a single group of three female Wistar rats was dosed with [3-^{14}C]quinclorac methyl ester (specific activity 71.3 Bq/µg; radiochemical purity 94%) by gavage in 1:1 Tween:ethanol at 50 mg/kg bw. Urine was collected at 8, 24, 48, 72, 96 and 120 hours. Faeces were collected at 24, 48, 72, 96 and 120 hours. Samples were processed and analysed by LSC. In the first 24 hours, 89% of the dose was excreted in the urine (66%) and faeces (24%). In total, 68% of the dose was recovered in the urine, with 32% of the dose recovered in the faeces (Parker, 1998).

The absorption, distribution and excretion of [3-^{14}C]quinclorac methyl ester (batch no. 753-1101; radiochemical purity 99.8%) were investigated in male bile duct–cannulated Wistar rats following a gavage dose at 15 or 600 mg/kg bw. Samples of urine, faeces, bile and tissues were

processed and analysed by LSC. Recovery was low (87%) at 15 mg/kg bw; the majority of the radiolabel was excreted within 24 hours, with 51% of the administered dose in urine and 30% in bile. At 600 mg/kg bw, excretion was slower, predominantly between 24 and 48 hours post-dosing, with the majority in bile (51%) and lesser amounts in urine (32%) and faeces (13%). Less than 1% of the administered radiolabel was detected in the carcass at 72 hours (Fabian & Landsiedel, 2011; Fabian, 2012).

Biotransformation

Urine and faecal samples in the study by Parker (1998) were extracted and analysed by high-performance liquid chromatography (HPLC). Only one major peak was identified in the majority of urine samples, which corresponded to quinclorac (approximately 80% of the radiolabel in the 8-hour sample). A secondary peak identified in the 24-hour urine sample was identified as quinclorac glucuronide following glucuronidase treatment. The faecal samples contained a multitude of metabolites, each less than 1.4% of the administered dose, which were not identified.

The biotransformation of quinclorac methyl ester was investigated using samples from the study of Fabian & Landsiedel (2011). Pooled samples of bile, urine and faeces were extracted and analysed by HPLC. At the low dose (15 mg/kg bw), there was no detectable quinclorac methyl ester in bile or urine; in faeces, quinclorac methyl ester represented only 0.45% of the administered dose. The predominant metabolite was quinclorac, representing 50% of the administered dose. At 600 mg/kg bw, the methyl ester represented 12% of the administered dose, and quinclorac, 17% (Thiaener, Glaessgen & Deppermann, 2011). Additional investigations of the bile samples from the 600 mg/kg bw group, using techniques including liquid chromatography with tandem mass spectrometry and electrospray ionization, time-of-flight mass spectrometry), identified or characterized further metabolites representing approximately half the administered dose (their structures and levels are presented in Tables A5 and A6 in Appendix 1) (Thiaener, Glaessgen & Deppermann, 2012).

A metabolic pathway for quinclorac methyl ester has been proposed, involving one or more of these primary steps:

- demethylation;
- glutathione conjugation at the chlorine on position 7; and
- arene oxide formation.

This can be followed by:

- glucuronidation;
- degradation and transformation of the glutathione moiety;
- hydroxylation of the quinoline ring structure; and
- dimerization.

Acute toxicity

Two groups of three female Wistar rats were administered quinclorac methyl ester (batch no. L84-18; purity 99.6%) by gavage in 0.5% carboxymethyl cellulose at 2000 mg/kg bw. Clinical signs, including dyspnoea, poor general state and piloerection, were seen, but there were no deaths. The acute oral LD_{50} was greater than 2000 mg/kg bw (Cords & Lammer, 2010).

Short-term studies of toxicity

Groups of 10 male and 10 female Wistar (Crl:WI(Han)) rats were given diets containing quinclorac methyl ester (batch no. L84-18; purity 99.6%) at a dose level of 0, 2000, 4000 or 8000 ppm for 3 months. Achieved test article intakes were 0, 128, 252 and 518 mg/kg bw per day for males and 0, 145, 274 and 509 mg/kg bw per day for females, respectively. Clinical signs, body weight and feed consumption were monitored regularly. Samples for clinical chemistry and haematology were

taken on day 92. Urine analysis samples were obtained on day 90. Ophthalmoscopy was performed on animals in the control and top-dose groups pretest and on day 90. A functional observational battery, including motor activity assessments, was performed on day 85. All animals were subjected to gross pathological examination followed by a microscopic examination. Control and top-dose animals received a full microscopic examination; for the low- and intermediate-dose groups, only thyroids, liver, kidneys and gross lesions were examined. Additional staining techniques were used on selected kidney samples.

There were no mortalities or treatment-related effects in the functional observational battery, ophthalmoscopy, haematology or urine analysis results. Discoloured urine, possibly due to excretion of test material (a beige powder), was reported at 4000 and 8000 ppm (Table 22). Body weights were reduced from day 7 onwards (Table 22) in both sexes receiving 8000 ppm and from day 21 in males receiving 4000 ppm. Feed consumption was consistently reduced in the 4000 and 8000 ppm groups. A number of clinical chemistry parameters were altered in top-dose animals (Table 22). The increased gamma-glutamyltranspeptidase (GGT) activity in top-dose males is indicative of liver toxicity. Although the inorganic phosphorus levels exhibit a dose-related increase, all values are within the normal range seen in the test laboratory. Absolute liver weights were significantly increased in males in the high-dose group (117%) and in females in all treatment groups (110%, 111% and 117% at 2000, 4000 and 8000 ppm, respectively). Absolute kidney weight in low-dose males (109%) and absolute adrenal gland weight in low-dose females (114%) were significantly increased, but these findings were not reproduced at higher dose levels and therefore are considered unrelated to quinclorac administration. The mean relative weights of the liver of animals in all treatment groups and of the thyroid glands of males in all treatment groups were significantly increased (Table 22) and are regarded as treatment-related effects. The significantly increased relative weights of adrenal glands, brain, epididymides, kidneys, spleen, thymus and testes are considered secondary to the decreased terminal body weights and not adverse in isolation.

Gross lesions of the liver (dark coloration and enlarged) were seen in treated males, but with no clear dose–response relationship or histopathological correlations. Histopathological changes included minimal to slight hepatocellular hypertrophy in male and female animals of all treatment groups (Table 22). In the thyroid gland of all treatment groups, an increased incidence of minimal to slight follicular hypertrophy/hyperplasia was evident (Table 22). The kidneys of treated males showed a "nuclear crowding" of tubular epithelial cells at the corticomedullary junction, increasing in incidence and degree of severity with dose. Immunohistochemical staining demonstrated an early cellular injury in affected areas (positive with the antibody against kidney injury molecule [KIM] antigen), but no increased proliferation rates (proliferating cell nuclear antigen [PCNA] and Ki-67 staining). No staining for α_{2u}-globulin was performed. There were no specific investigations of hepatic microsomal enzyme activity or thyroid hormones.

The authors of the study report proposed that the findings seen at the low dose levels were not adverse and/or not relevant to humans:

- The increased liver weight and hyperplasia are adaptive and related to increased microsomal enzyme activity.
- The increased thyroid weights and hyperplasia/hypertrophy are secondary to enhanced thyroid hormone clearance as a result of increases in uridine diphosphate-glucuronosyltransferase (UGT) activity.
- The kidney lesions are seen only in males and therefore are related to rat-specific chronic progressive nephropathy.

However, there are no specific data to support these contentions, and the suggestion that they are not treatment-related adverse findings is not accepted.

A NOAEL cannot be identified for this study owing to the presence of increased relative liver weights and hepatocellular hypertrophy, increased relative thyroid gland weights and hypertrophy/hyperplasia, and "nuclear crowding" of the kidney at 2000 ppm (equal to 128 mg/kg bw per day), the lowest dose tested (Buesen et al., 2011).

Table 22. Findings in rats receiving quinclorac methyl ester for 90 days

	Males				Females			
Observation	**0 ppm**	**2 000 ppm**	**4 000 ppm**	**8 000 ppm**	**0 ppm**	**2 000 ppm**	**4 000 ppm**	**8 000 ppm**
Occurrence of observation (%)								
Discoloured urine	0	0	100	100	0	0	100	100
Clinical chemistry (group mean values)								
GGT (nkat/L)	0	0	1	11**	2	1	5	2
Cholesterol (mmol/L)	1.98	2.26	2.91	2.57	1.36	1.58	1.88**	2.20**
Triglycerides (mmol/L)	0.85	0.86	0.79	0.42**	0.44	0.42	0.47	0.95**
Total bilirubin (µmol/L)	1.54	1.3	1.32	1.22	1.97	1.71	1.70	1.50**
Inorganic phosphate (mmol/L)	1.53	1.67*	1.70*	1.73*	1.20	1.17	1.34	1.41
Body weights (group mean values)								
Terminal body weight (g)	407.4	390.8	351.7**	340.8**	220.2	213.6	205.9	192.3**
Relative organ weights (% of body weight)								
Adrenal glands	0.014	0.015*	0.018**	0.018**	0.033	0.039**	0.035	0.033
Brain	0.516	0.523	0.577*	0.591**	0.863	0.900	0.925*	0.983**
Epididymides	0.271	0.299	0.318**	0.329**	–	–	–	–
Kidneys	0.578	0.657**	0.641	0.706**	0.683	0.703	0.742	0.733
Liver	2.165	2.476**	2.765**	3.038**	2.209	2.512**	2.627**	2.968**
- % of control	100	114	128	140	100	114	119	134
Testes	0.839	0.951*	1.018**	1.038**	–	–	–	–
Thyroid glands	0.005	0.007**	0.007*	0.007**	0.007	0.009	0.008	0.009
Incidence of microscopic findings in liver								
Hypertrophy (total)	0	5	9	10	0	3	6	10
Hypertrophy, centrilobular								
- Grade 1	0	0	0	0	0	3	4	1
- Grade 2	0	0	0	0	0	0	0	1
Hypertrophy, centrilobular to intermediate								
- Grade 1	0	5	2	0	0	0	2	0

Observation	Males				Females			
	0 ppm	2 000 ppm	4 000 ppm	8 000 ppm	0 ppm	2 000 ppm	4 000 ppm	8 000 ppm
- Grade 2	0	0	7	6	0	0	0	9
Hypertrophy, diffuse (grade 2)	0	0	0	4	0	0	0	0
Incidence of microscopic findings in thyroid glands								
Hypertrophy/ hyperplasia follicular								
- Grade 1	1	1	5	1	0	1	0	2
- Grades 2–4	0	1	2	7	0	1	6	8
Incidence of microscopic findings in kidneys								
Nuclear crowding	0	9	9	10	0	0	0	0
- Grade 1	–	6	4	–	–	–	–	–
- Grade 2	–	3	3	4	–	–	–	–
- Grade 3	–	–	2	6	–	–	–	–

GGT: gamma-glutamyltranspeptidase; ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$
Source: Buesen et al. (2011)

The pattern of toxicity seen with the methyl ester is not the same as that seen with quinclorac; therefore, a comparison of relative toxic potency is not straightforward. A comparison of the 90-day studies of toxicity in rats for quinclorac and quinclorac methyl ester results in a ratio of 2.4 (302/128) between the NOAEL for quinclorac and the LOAEL for the ester and a ratio of 7.3 (930/128) between the LOAEL for quinclorac and the LOAEL for the ester. The main metabolic step of the methyl ester is demethylation to quinclorac, which suggests that some aspects of the toxicity of the methyl ester will have been addressed by studies with quinclorac. In acute oral toxicity studies, similar clinical signs (poor general state, dyspnoea, piloerection) were reported at a dose of 2000 mg/kg bw for the methyl ester and a similar dose of 1780 mg/kg bw used in the oral LD_{50} study with quinclorac (Grundler & Kirsch, 1983a). The Meeting concluded that quinclorac methyl ester was likely to be less than 10-fold more toxic than quinclorac.

Several quinclorac conjugates were identified as plant metabolites. No specific toxicity data were available on these conjugates, but a structure–activity relationship (SAR) analysis (DEREK) identified no alerts that were not also present for quinclorac. It is expected that these conjugates will readily hydrolyse to the parent in the gastrointestinal tract. Therefore, it is expected that quinclorac conjugates will be of lower or equivalent toxicity compared with quinclorac.

3. Observations in humans

The facility that produces quinclorac also produces the closely related compound quinmerac. The production facility for quinclorac was designed as a closed system and is controlled by automation, with all the gas/dust and wastewater collected and incinerated at the production site. Given the design of the plant, the likelihood of exposure is low.

Currently, there are 41 people who work in the quinclorac production plant, including seven who work in the analysis laboratory. There is an annual medical examination for all the employees. In addition to a general medical examination, some workers will have additional testing as determined by the chemicals they handle in their daily work. To date, there have been no reports of exposure-related abnormal medical examinations in employees in the quinclorac production plant (Riffle, 2015).

Comments

Biochemical aspects

The toxicokinetics and biotransformation of quinclorac were investigated in rats administered (2,3,4-^{14}C)-labelled quinclorac at a single dose of 15, 100, 600 or 1200 mg/kg bw by gavage or at 15 000 ppm in the diet (equivalent to 1200 mg/kg bw); 7 daily doses of 15 or 600 mg/kg bw per day by gavage or at 15 000 ppm in the diet (equivalent to 1200 mg/kg bw per day); or 14 daily doses of 15 mg/kg bw per day of unlabelled quinclorac followed by a single labelled dose of 15 mg/kg bw. Absorption was rapid, with maximal blood concentrations achieved between 0.25 and 1 hour for single doses of 600 mg/kg bw and below. The extent of oral absorption was high (> 90%) at all dose levels, based on urinary and biliary data, with some of the biliary component being reabsorbed. Quinclorac was widely distributed in the body, with highest concentrations of radiolabel present in the blood, kidney and plasma. The labelled material was excreted primarily via urine (50–90% in 24 hours). Clearance from the blood was slower following repeated dosing with 600 mg/kg bw and a single dose of 1200 mg/kg bw, resulting in non-proportionate increases in AUC with dose. Absorbed quinclorac was metabolized to only a limited extent, with unchanged parent compound representing approximately 80% of the excreted radiolabel. The major biotransformation product was quinclorac–glucuronide conjugate, at approximately 5% of the administered dose. The excretion pattern, tissue distribution of radioactivity and/or metabolite profile were similar across administered dose levels and with single or repeated administration (Hawkins et al., 1986, 1987).

Toxicological data

Quinclorac was of low acute toxicity in rats via the oral route (LD_{50} = 2680 mg/kg bw) (Grundler & Kirsch, 1983a) or dermal route (LD_{50} > 2000 mg/kg bw) (Grundler & Kirsch, 1983b) and by inhalation (LC_{50} > 5.15 mg/L air) (Klimisch, 1986). Quinclorac was not irritating to the skin of rabbits (Grundler & Kirsch, 1983c), but was transiently and mildly irritating to the eyes of rabbits (Grundler & Kirsch, 1983d). Modern material of a high purity (99.4%) was not a skin sensitizer in guinea-pigs (Gamer & Leibold, 2005d), but a positive result was seen with older, less pure (97.4%) quinclorac (Kieczka, 1986).

In repeated-dose toxicity studies in mice, rats and dogs, the predominant effect was reduced body weight gain, often associated with reductions in feed consumption. The only organ showing consistency of effects was the kidney, with increases in organ weight and histopathological changes (e.g. interstitial nephritis) at high dose levels.

In a 90-day study of toxicity in mice, dietary concentrations of quinclorac were 0, 4000, 8000 and 16 000 ppm (equal to 0, 1001, 1992 and 4555 mg/kg bw per day for males and 0, 1466, 2735 and 5953 mg/kg bw per day for females, respectively). The NOAEL was 4000 ppm (equal to 1001 mg/kg bw per day), based on increases in blood urea levels and water consumption at 8000 ppm (equal to 1992 mg/kg bw per day). Slight changes in body weight and mean red blood cell volume were considered not to be adverse (Kuehborth et al., 1988).

In a subsequent 90-day dietary study of toxicity in mice administered 500 ppm quinclorac (equal to 85 mg/kg bw per day for males and 130 mg/kg bw per day for females), there were no treatment-related effects; the NOAEL was 500 ppm (equal to 85 mg/kg bw per day), the only dose tested (Schilling et al., 1988a).

In a 90-day study of toxicity in rats, dietary concentrations of quinclorac were 0, 1000, 4000 and 12 000 ppm (equal to 0, 77, 302 and 930 mg/kg bw per day for males and 0, 87, 358 and 1035 mg/kg bw per day for females, respectively). The NOAEL was 4000 ppm (equal to 302 mg/kg bw per day), on the basis of a range of clinical chemistry and haematology changes in both sexes and urothelial hyperplasia and interstitial nephritis in males at 12 000 ppm (equal to 930 mg/kg bw per day) (Kuehborth, Deckardt & Hildebrand, 1986).

In a 28-day dietary study in which dogs were administered quinclorac at 0, 1000, 3000, 9000 or 27 000 ppm (equal to 0, 31, 95, 278 and 912 mg/kg bw per day for males and 0, 36, 108, 315 and 956 mg/kg bw per day for females, respectively), the NOAEL was 9000 ppm (equal to 278 mg/kg bw per day), based on body weight loss and kidney lesions at 27 000 ppm (equal to 912 mg/kg bw per day) (Hellwig et al., 1985).

In a 1-year study in dogs in which quinclorac was administered in the diet at 0, 1000, 4000 or 12 000 ppm (equal to 0, 35, 139 and 490 mg/kg bw per day for males and 0, 35, 141 and 472 mg/kg bw per day for females, respectively), the NOAEL was 1000 ppm (equal to 35 mg/kg bw per day), on the basis of an increase in relative kidney weight in males at 4000 ppm (equal to 139 mg/kg bw per day) (Hellwig et al., 1988a).

In a 78-week toxicity and carcinogenicity study in mice, dietary concentrations of quinclorac were 0, 1000, 4000 and 8000 ppm (equal to 0, 170, 711 and 1444 mg/kg bw per day for males and 0, 213, 869 and 1828 mg/kg bw per day for females, respectively). No NOAEL could be identified, as reductions in body weight were observed in females at all doses. Quinclorac did not produce any increase in the incidences of benign or malignant tumours (Schilling et al., 1988c).

A subsequent 78-week toxicity study in mice used a single dietary level of 250 ppm (equal to 42 mg/kg bw per day for males and 52 mg/kg bw per day for females). There were no adverse effects (Schilling et al., 1988d).

The Meeting concluded that the overall NOAEL for the 78-week toxicity studies in mice was 250 ppm (equal to 52 mg/kg bw per day), based on reductions in body weight in females at 1000 ppm (equal to 213 mg/kg bw per day).

In a 2-year toxicity and carcinogenicity study in rats, dietary concentrations of quinclorac were 0, 1000, 4000 and 8000 ppm (equal to 0, 55, 221 and 444 mg/kg bw per day for males and 0, 66, 262 and 529 mg/kg bw per day for females, respectively) for evaluation of carcinogenic potential. Satellite groups received diets containing quinclorac at 0, 1000, 4000, 8000 or 12 000 ppm (equal to 0, 55, 221, 444 and 675 mg/kg bw per day for males and 0, 66, 262, 529 and 832 mg/kg bw per day for females, respectively) for the evaluation of toxicity. The only significant effect was a decrease in the body weight of top-dose females in the satellite group. The NOAEL was 8000 ppm (equal to 529 mg/kg bw per day), on the basis of reductions in body weight in females at 12 000 ppm (equal to 832 mg/kg bw per day). Quinclorac did not increase the incidence of benign or malignant tumours (Schilling et al., 1988b).

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

Quinclorac was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. The majority of studies produced negative results. Positive results were seen at high concentrations in a cytogenicity assay in human lymphocytes (Gelbke & Engelhardt, 1986a). In vivo assays of bone marrow micronucleus induction (Gelbke & Engelhardt, 1986b) and unscheduled DNA synthesis in hepatocytes (Fautz & Voelkner, 1991) gave negative results.

The Meeting concluded that quinclorac is unlikely to be genotoxic in vivo.

In view of the fact that quinclorac is unlikely to be genotoxic in vivo and the absence of carcinogenicity in mice and rats, the Meeting concluded that quinclorac is unlikely to pose a carcinogenic risk to humans from the diet.

In a two-generation study of reproductive toxicity in rats, with two matings in the F_1 generation and one in the F_2 generation, dietary concentrations of quinclorac were 0, 1000, 4000 and

12 000 ppm (equivalent to mean intakes of 0, 96, 381 and 1180 mg/kg bw per day, respectively). The NOAEL for reproductive effects was 12 000 ppm (equivalent to 1180 mg/kg bw per day), the highest dose tested. The NOAEL for parental toxicity was 4000 ppm (equivalent to 381 mg/kg bw per day), based on an increase in the incidence of interstitial nephritis at 12 000 ppm (equivalent to 1180 mg/kg bw per day) in females of both generations. The NOAEL for effects on offspring was 4000 ppm (equivalent to 381 mg/kg bw per day), based on reduced pup weight during lactation at 12 000 ppm (equivalent to 1180 mg/kg bw per day) (Hellwig et al., 1988b).

In a study of developmental toxicity in rats dosed with quinclorac at 0, 24.4, 146 or 438 mg/kg bw per day by gavage in 0.5% carboxymethyl cellulose, there were no effects on any measured fetal parameters. The NOAEL for maternal toxicity was 146 mg/kg bw per day, on the basis of deaths, reduced feed intake, increased water intake and severe ulceration of the glandular stomach at 438 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 438 mg/kg bw per day, the highest dose tested (Hellwig, 1987).

In a study of developmental toxicity in rabbits dosed with quinclorac at 0, 70, 200 or 600 mg/kg bw per day by gavage in 0.5% carboxymethyl cellulose, severe maternal toxicity, including death, was observed at 600 mg/kg bw per day. Live pup numbers were reduced at 600 mg/kg bw per day. At the top dose level, there was an increase in the number of pups with skeletal variations, although there was no significant increase in any specific variation. There was no increase in the number of pups with malformations. The NOAEL for maternal toxicity was 200 mg/kg bw per day, based on mortality and body weight loss at 600 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 200 mg/kg bw per day, based on an increase in fetuses with skeletal variations, reduced numbers of viable fetuses and reduced fetal weights at 600 mg/kg bw per day (Hellwig, Hildebrand & Shirasu, 1988).

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

The acute neurotoxicity of quinclorac was investigated in rats administered dose levels of 0, 150, 500 or 1500 mg/kg bw by gavage in 1% carboxymethyl cellulose. Dose-related reductions in locomotor activity were seen at 4–5 hours post-dosing, but not subsequently, in the mid- and high-dose groups. Motor activity reductions in males in the low-dose group were considered not to be treatment related, as the background activity in this group was consistently lower than in the other groups. There were no indications of neuropathy. The NOAEL was 150 mg/kg bw, based on reduced motor activity at 500 mg/kg bw (Buesen et al., 2012a).

In a subchronic (90-day) neurotoxicity study in rats, dietary concentrations of quinclorac were 0, 1500, 5000 and 15 000 ppm (equal to 0, 96, 301 and 976 mg/kg bw per day for males and 0, 112, 368 and 1142 mg/kg bw per day for females, respectively). No adverse effects were reported. The NOAEL for neurotoxicity was 15 000 ppm (equal to 976 mg/kg bw per day), the highest dose tested (Buesen et al., 2012b).

The reduced motor activity seen in the acute neurotoxicity study is a relatively general finding, not specific to a neurotoxic mode of action; there was no evidence of specific neurotoxic findings in other studies. The Meeting concluded that quinclorac is not neurotoxic.

In a 28-day immunotoxicity study in female mice, dietary concentrations were 0, 500, 1500 and 5000 ppm (equal to 0, 176, 439 and 1760 mg/kg bw per day, respectively). No adverse effects were reported. The NOAEL for immunotoxicity was 5000 ppm (equal to 1760 mg/kg bw per day), the highest dose tested (Buesen et al., 2010).

The Meeting concluded that quinclorac is not immunotoxic.

Biochemical and toxicological data on metabolites and/or degradates

[3-^{14}C]Quinclorac methyl ester, a plant metabolite, administered to rats at 15, 50 or 600 mg/kg bw by gavage was rapidly and extensively absorbed and excreted via urine and bile. The proportion of radiolabel in the bile increased from 30% at 15 mg/kg bw to 51% at 600 mg/kg bw, with

a corresponding decrease in radiolabel in urine (51% and 32%, respectively) (Fabian & Landsiedel, 2011). The initial steps in biotransformation involved extensive demethylation to release free quinclorac (approximately 50% of the administered dose) (Parker, 1998; Thiaener, Glaessgen & Deppermann, 2011). Other metabolic steps, identified from biliary metabolites, were arene oxide formation and conjugation with glutathione, with subsequent transformation of the glutathione moiety, hydroxylation of the quinoline structure and dimerization (Thiaener, Glaessgen & Deppermann, 2012).

Quinclorac methyl ester has a low acute oral toxicity to rats (LD_{50} > 2000 mg/kg bw); clinical signs (poor general state, dyspnoea and piloerection) were noted (Cords & Lammer, 2010).

In a repeated-dose study of toxicity in rats, quinclorac methyl ester was administered in the diet at 0, 2000, 4000 or 8000 ppm (equal to 0, 128, 252 and 518 mg/kg bw per day for males and 0, 145, 274 and 509 mg/kg bw per day for females, respectively) for 3 months. The main findings were reduced body weight, increased relative organ weights and histopathological changes of the liver, thyroid and kidney. A NOAEL could not be identified, as increased relative liver weights, hepatocellular hypertrophy, increased relative thyroid gland weights, thyroid hypertrophy/hyperplasia and "nuclear crowding" of the kidney were observed at 2000 ppm (equal to 128 mg/kg bw per day), the lowest dose tested (Buesen et al., 2011).

The pattern of toxicity seen with the methyl ester is not the same as that seen with quinclorac; therefore, a comparison of relative toxic potency is not straightforward. A comparison of the 90-day studies of toxicity in rats for quinclorac and quinclorac methyl ester results in a ratio of 2.4 (302/128) between the NOAEL for quinclorac and the LOAEL for the ester and a ratio of 7.3 (930/128) between the LOAEL for quinclorac and the LOAEL for the ester. The main metabolic step of the methyl ester is demethylation to quinclorac, which suggests that some aspects of the toxicity of the methyl ester will have been addressed by studies with quinclorac. In acute oral toxicity studies, similar clinical signs (poor general state, dyspnoea, piloerection) were reported at a dose of 2000 mg/kg bw for the methyl ester and a similar dose of 1780 mg/kg bw used in the oral LD_{50} study with quinclorac (Grundler & Kirsch, 1983a). The Meeting concluded that quinclorac methyl ester was likely to be less than 10-fold more toxic than quinclorac.

Several quinclorac conjugates were identified as plant metabolites. No specific toxicity data were available on these conjugates, but a SAR analysis identified no alerts that were not also present for quinclorac. The Meeting concluded that these conjugates were likely to be of lower or equivalent toxicity compared with the parent compound, because they are expected to be readily hydrolysed to the parent in the gastrointestinal tract.

Human data

No adverse effects have been reported in quinclorac production and formulation plant workers, and no significant effects have been reported in exposed users of quinclorac-based products (Riffle, 2015).

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) for quinclorac of 0–0.4 mg/kg bw, on the basis of the NOAEL of 35 mg/kg bw per day for increased relative kidney weights from the 1-year dog study. A safety factor of 100 was applied.

The Meeting established an acute reference dose (ARfD) for quinclorac of 2 mg/kg bw, on the basis of the NOAEL of 150 mg/kg bw per day for reductions in motor activity in the acute neurotoxicity study in rats. A safety factor of 100 was applied.

The plant metabolite quinclorac methyl ester is not found in rats administered quinclorac. The main metabolic step for the methyl ester in rats is demethylation to quinclorac. Similar clinical signs were seen at similar doses in the acute oral toxicity studies with quinclorac and the methyl ester. In a 90-day study of toxicity in rats, the methyl ester produced a pattern of liver, kidney and thyroid effects that differed from that seen in the equivalent study with quinclorac, and the LOAEL for the methyl ester was below the NOAEL for quinclorac.

The Meeting concluded that the methyl ester is likely to be less than 10-fold more toxic than quinclorac, that a 10-fold potency factor should be applied to the residue levels for use in both the acute and chronic dietary exposure estimates for quinclorac and that these should be added to the acute and chronic dietary exposures for quinclorac and compared with the ARfD and ADI for quinclorac, respectively.

The Meeting concluded that the quinclorac conjugates were of no greater toxicity than the parent.

Both the ADI and ARfD are established for the sum of quinclorac and its conjugates, and quinclorac methyl ester (×10), expressed as quinclorac.

Levels relevant to risk assessment of quinclorac and quinclorac methyl ester

Species	Study	Effect	NOAEL	LOAEL
Mouse	Seventy-eight-week studies of toxicity and carcinogenicity[a,b]	Toxicity	250 ppm, equal to 52 mg/kg bw per day	1 000 ppm, equal to 213 mg/kg bw per day
		Carcinogenicity	8 000 ppm, equal to 1 444 mg/kg bw per day[c]	–
Rat	Acute neurotoxicity study[d]	Neurotoxicity	150 mg/kg bw	500 mg/kg bw
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	8 000 ppm, equal to 529 mg/kg bw per day	12 000 ppm, equal to 832 mg/kg bw per day
		Carcinogenicity	8 000 ppm, equal to 444 mg/kg bw per day[c]	–
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	12 000 ppm, equivalent to 1 180 mg/kg bw per day[c]	–
		Parental toxicity	4 000 ppm, equivalent to 381 mg/kg bw per day	12 000 ppm, equivalent to 1 180 mg/kg bw per day
		Offspring toxicity	4 000 ppm, equivalent to 381 mg/kg bw per day	12 000 ppm, equivalent to 1 180 mg/kg bw per day
	Developmental toxicity study[d]	Maternal toxicity	146 mg/kg bw per day	438 mg/kg bw per day
		Embryo and fetal toxicity	438 mg/kg bw per day[c]	–
Rabbit	Developmental toxicity study[d]	Maternal toxicity	200 mg/kg bw per day	600 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
		Embryo and fetal toxicity	200 mg/kg bw per day	600 mg/kg bw per day
Dog	One-year study of toxicity[a]	Toxicity	1 000 ppm, equal to 35 mg/kg bw per day	4 000 ppm, equal to 139 mg/kg bw per day
Metabolite: Quinclorac methyl ester				
Rat	Ninety-day study of toxicity	Toxicity	–	2 000 ppm, equal to 128 mg/kg bw per day[e]

[a] Dietary administration.
[b] Two or more studies combined.
[c] Highest dose tested.
[d] Gavage administration.
[e] Lowest dose tested.

Estimate of acceptable daily intake (ADI) for the sum of quinclorac and its conjugates, and quinclorac methyl ester (×10), expressed as quinclorac

0–0.4 mg/kg bw

Estimate of acute reference dose (ARfD) for the sum of quinclorac and its conjugates, and quinclorac methyl ester (×10), expressed as quinclorac

2 mg/kg bw

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 quinclorac

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid (T_{max} = 0.25–1 h) and extensive (> 90%)
Dermal absorption	No data
Distribution	Widely distributed; highest levels in blood, kidney and plasma
Potential for accumulation	None
Rate and extent of excretion	Rapid (up to 90% excreted in urine within 24 h)
Metabolism in animals	Limited; 80% excreted unchanged; some glucuronidation
Toxicologically significant compounds in animals and plants	Quinclorac; quinclorac methyl ester; conjugates
Acute toxicity	
Rat, LD_{50}, oral	2 680 mg/kg bw
Rat, LD_{50}, dermal	> 2 000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.15 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Mildly, transiently irritating

Guinea-pig, dermal sensitization	Negative (maximization test)
Short-term studies of toxicity	
Target/critical effect	Reduced body weights; increased kidney weight, interstitial nephritis, urothelial hyperplasia
Lowest relevant oral NOAEL	35 mg/kg bw per day (12 months; dog)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day (rabbit; highest dose tested)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Reduced body weight
Lowest relevant NOAEL	52 mg/kg bw per day (mouse)
Carcinogenicity	Not carcinogenic in mice or rats[a]
Genotoxicity	
	Unlikely to be genotoxic in vivo[a]
Reproductive toxicity	
Target/critical effect	No effects on reproduction; reduced pup weight during lactation
Lowest relevant parental NOAEL	381 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	381 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	1 180 mg/kg bw per day (rat; highest dose tested)
Developmental toxicity	
Target/critical effect	No effects in rats; reduction in viable fetuses, decreased fetal weight, increase in skeletal variations (rabbit)
Lowest relevant maternal NOAEL	146 mg/kg bw per day (rat)
Lowest relevant embryo/fetal NOAEL	200 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	150 mg/kg bw (decreased motor activity; rat)
Subchronic neurotoxicity NOAEL	976 mg/kg bw per day (rat; highest dose tested)
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity NOAEL	1 760 mg/kg bw per day (mouse; highest dose tested)
Studies on toxicologically relevant metabolites	*Quinclorac methyl ester* Rapidly and extensively absorbed. Initial step in metabolism is demethylation to quinclorac. Acute oral LD_{50} > 2 000 mg/kg bw LOAEL in 90-day rat study = 128 mg/kg bw per day (lowest dose tested), based on kidney, liver and thyroid effects
Medical data	
	No adverse effects reported in humans

[a] Unlikely to pose a carcinogenic risk to humans from the diet.

Summary

	Value	Study	Safety factor
ADI	0–0.4 mg/kg bw	One-year toxicity study (dog)	100
ARfD	2 mg/kg bw	Acute neurotoxicity study (rat)	100

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Appendix 1. Supplementary tables

Table A1. Historical control data for pancreatic lesions in rats: hyperplasia

Study	No. observed per sex	Males		Females	
		Frequency	%	Frequency	%
8116	50	0	0.0	0	0.0
8240	50	4	8.0	0	0.0
8241	50	0	0.0	0	0.0
8249	50	13	26.0	0	0.0
8345	50	0	0.0	0	0.0
8352	50	6	12.0	0	0.0
8424	98/100	8	8.2	3	3.0
8425	20	0	0.0	0	0.0
8519	50	3	6.0	1	2.0
8519	20	1	5.0	1	5.0
8583	20	0	0.0	0	0.0
8584	50	0	0.0	0	0.0
8591	20	0	0.0	1	5.0
8592	50	0	0.0	0	0.0
8604	50	4	8.0	1	2.0
87046	20	1	5.0	0	0.0

Study	No. observed per sex	Males		Females	
		Frequency	%	Frequency	%
87047	50	1	2.0	0	0.0
Sum	748/750	41	80.2	7	17.0
Mean	–	–	4.7	–	1.1
Median	–	–	2.0	–	0.0

Source: Schilling et al. (1988); Riffle (2015)

Table A2. Historical control data for pancreatic lesions in rats: adenoma and adenocarcinoma

Study	No. observed per sex	Males				Females			
		Adenoma		Adenocarcinoma		Adenoma		Adenocarcinoma	
		Frequency	%	Frequency	%	Frequency	%	Frequency	%
8116	50	0	0.0	0	0.0	1	2.0	1	0.0
8240	50	0	0.0	0	0.0	1	2.0	0	0.0
8241	50	4	8.0	0	0.0	0	0.0	0	0.0
8249	50	2	4.0	0	0.0	0	0.0	0	0.0
8345	50	9	18.0	1	2.0	4	8.0	0	0.0
8352	50	0	0.0	0	0.0	0	0.0	0	0.0
8424	98/100	9	9.2	5	5.1	1	1.0	0	0.0
8425	20	0	0.0	0	0.0	0	0.0	0	0.0
8519	50	0	0.0	0	0.0	0	0.0	0	0.0
8519	20	0	0.0	1	5.0	0	0.0	0	0.0
8583	20	1	5.0	0	0.0	0	0.0	0	0.0
8584	50	4	8.0	0	0.0	1	2.0	0	0.0
8591	20	1	5.0	0	0.0	0	0.0	0	0.0
8592	50	1	2.0	0	0.0	0	0.0	0	0.0
8604	50	8	16.0	0	0.0	0	0.0	0	0.0
87046	20	0	0.0	0	0.0	0	0.0	0	0.0
87047	50	0	0.0	0	0.0	0	0.0	0	0.0
Sum	748/750	39	–	7	–	8	–	1	–
Mean	–	–	4.4	–	0.7	–	0.9	–	0.1
Median	–	–	5.0	–	0.0	–	0.0	–	0.0

Source: Schilling et al. (1988); Riffle (2015)

Table A3. Cytogenetics assay in human lymphocytes

	Without S9 mix						With S9 mix					
	0 µg/L	DMSO	250 µg/L	500 µg/L	1 000 µg/L	MMC	0 µg/L	DMSO	500 µg/L	1 000 µg/L	2 000 µg/L	CP
Analysed metaphases	200	200	200	200	200	100	200	200	200	200	200	100
Aberrant	5	5	13	19	29	62	11	7	10	14	21	27

	Without S9 mix						With S9 mix					
	0 µg/L	DMSO	250 µg/L	500 µg/L	1 000 µg/L	MMC	0 µg/L	DMSO	500 µg/L	1 000 µg/L	2 000 µg/L	CP
metaphases including gaps												
Aberrant metaphases excluding gaps	1	2	3	3	18	58	2	1	2	3	8	19
Metaphases with exchanges	–	1	–	–	–	26	–	–	1		4	4
Polyploidy	1	1	2	2	1	–	4	–	1	1	10	1

CP: cyclophosphamide; DMSO: dimethyl sulfoxide; MMC: mitomycin C; S9: 9000 × *g* supernatant fraction from rat liver homogenate
Source: Gelbke & Engelhardt (1986)

Table A4. Gene mutation in mammalian cell gene mutation (second assay), with metabolic activation

Concentration (mg/mL)	Mutagenicity (number of colonies 7 days after seeding)					MR	MR		Cytotoxicity[a]			
							a	b	a		b	
									CE	%	CE	%
0	0	0	0	0	0	0	0	0	206/195	100.25	195/217	103.00
DMSO	1	0	0	1	1	2	2.27	2.08	196/156	88.00	190/195	96.25
0.0464	0	0	0	0	0	0	0	0	188/204	98.00	160/193	88.25
0.1	0	0	0	0	0	0	0	0	201/199	100.00	210/219	107.25
0.215	0	0	0	0	0	0	0	0	146/165	77.75	195/209	101.00
0.464	1	0	1	1	1	2.67	3.33	2.73	153/167	80.00	195/196	97.75
1.0	1	1	1	2	3	5.33	8.89	5.32	117/123	60.00	205/196	100.25
2.15	0	0	0	0	0	0	0	0	0/0	0	0	0
MCA 0.01	18	13	23	19	20	62.00	64.08	64.42	210/177	96.75	191/194	96.25

CE: cloning efficiency; DMSO: dimethyl sulfoxide; MCA: methylcholanthrene, positive control; MR: mutation rate
[a] "a" is for cytotoxicity based on cloning efficiency at 18–20 hours post-exposure; "b" is for cytotoxicity based on cloning efficiency at the end of the expression period.
Source: Jaeckh & Hoffmann (1990)

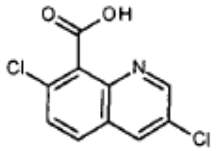
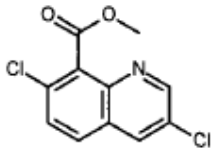
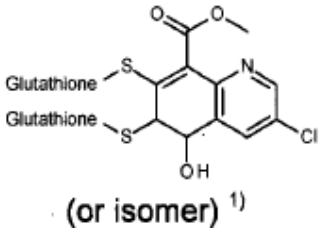
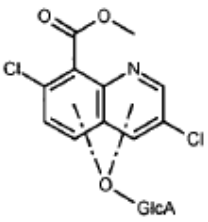
Table A5. Metabolites found in the bile of rats administered quinclorac methyl ester (600 mg/kg bw)

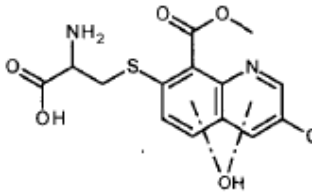
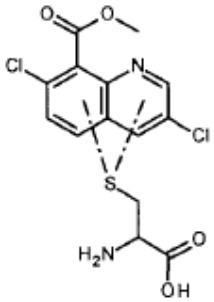
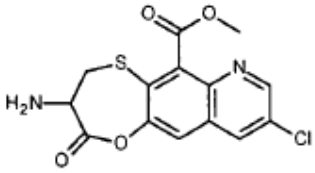
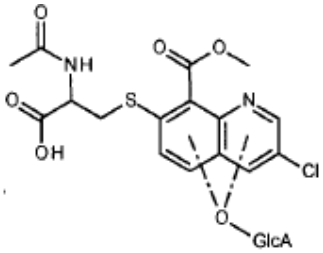
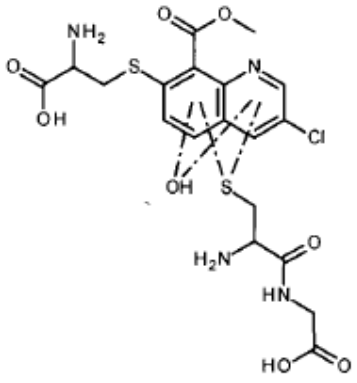
Designation of metabolite / peak (structures are in Table A6)	% TRR	% of dose
TRR (sample no. Lab0001)	100.00	46.56
Identified		
SES16382	5.69	2.65
SES16466 / SES16468 / SES16470	6.53	3.04

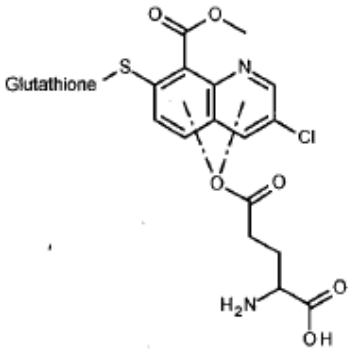
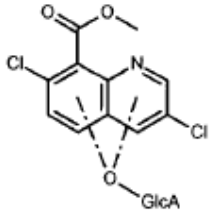
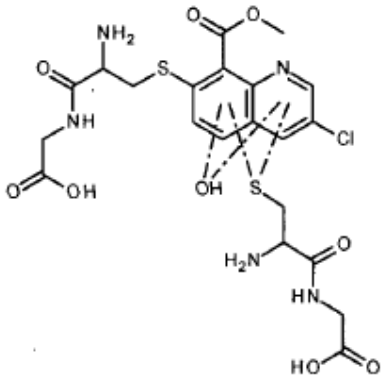
Designation of metabolite / peak (structures are in Table A6)	% TRR	% of dose
SES16442 / SES16458 / SES16454	21.47	10.00
SES16450 / SES16448 / SES16456	15.67	7.30
SES16438 and its isomer SES16452 / SES 16446 / MW = 443	5.81	2.70
Reg. No. 150732 (BAS 514 H)	1.61	0.75
Total identified	56.78	26.44
Characterized		
MW = 824 (dimer of SES16458), $C_{32}H_{30}Cl_2N_6O_{12}S_2$	6.84	3.19
28 further HPLC peaks (each below or equal to 1.88% of the dose)	36.38	16.94
Total characterized	43.22	20.12
Total identified and/or characterized	**100.00**	**46.56**

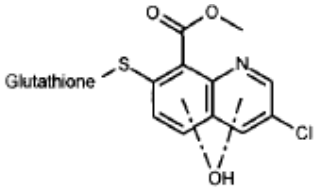
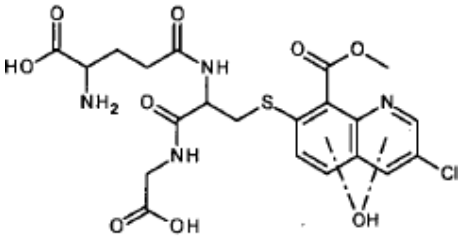
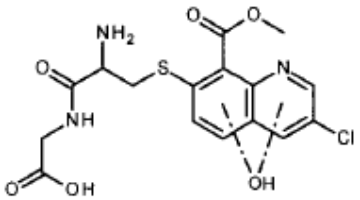
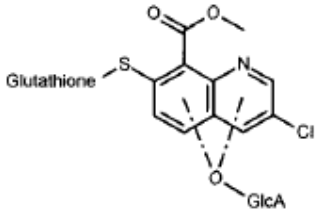
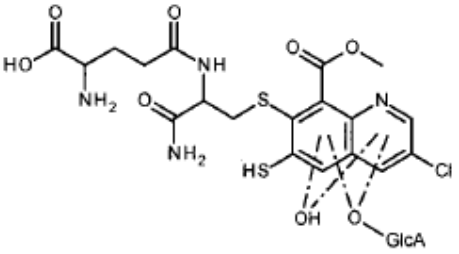
bw: body weight; HPLC: high-performance liquid chromatography; MW: molecular weight; TRR: total radioactive residue (in bile)
Source: Thiaener, Glaessgen & Deppermann (2012)

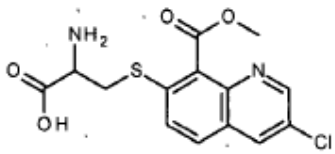
Table A6. Metabolites of ^{14}C-labelled quinclorac methyl ester identified or characterized in bile after oral administration to male rats

Metabolite code	Molecular formula	Nominal mass	Sample no.	Structural formula
SES1556 BAS 514 H Reg. No. 150732	$C_{10}H_5Cl_2NO_2$	241		
SES218 BH 514-Me Reg. No. 161555	$C_{11}H_7Cl_2NO_2$	255		
SES16382	$C_{31}H_{40}ClN_7O_{15}S_2$	849	Lab0005	 (or isomer) [1]
SES16438	$C_{17}H_{15}Cl_2NO_9$	447	Lab0007 and Lab0017	

Metabolite code	Molecular formula	Nominal mass	Sample no.	Structural formula
SES16440	$C_{14}H_{13}ClN_2O_5S$	356	Lab0017	 (or isomer) [1)]
SES16442	$C_{14}H_{12}Cl_2N_2O_4S$	374	Lab0007 and Lab0017	
SES16444	$C_{14}H_{11}ClN_2O_4S$	338	Lab0017	 (or isomer) [1)]
SES16446	$C_{22}H_{23}ClN_2O_{12}S$	574	Lab0007 and Lab0017	 (or isomer) [1)]
SES16448	$C_{19}H_{21}ClN_4O_8S_2$	532	Lab0007 and Lab0017	 (or isomer) [1)]

Metabolite code	Molecular formula	Nominal mass	Sample no.	Structural formula
SES16450	$C_{26}H_{30}ClN_5O_{12}S$	671	Lab0007 and Lab0017	 (or isomer) [1)]
SES16452	$C_{17}H_{15}Cl_2NO_9$	447	Lab0017	
SES16454	$C_{21}H_{24}ClN_5O_9S_2$	589	Lab0007 and Lab0017	 (or isomer) [1)]

Metabolite code	Molecular formula	Nominal mass	Sample no.	Structural formula
SES16456	$C_{21}H_{23}ClN_4O_9S$	542	Lab0007 and Lab0017	 (or isomer) [1)] i. e.  (or isomer) [1)]
SES16458	$C_{16}H_{16}ClN_3O_6S$	413	Lab0007 and Lab0017	 (or isomer) [1)]
SES16466	$C_{27}H_{31}ClN_4O_{15}S$	718	Lab0006	 (or isomer) [1)]
SES16468	$C_{25}H_{29}ClN_4O_{14}S_2$	708	Lab0006	 (or isomer) [1)]

Metabolite code	Molecular formula	Nominal mass	Sample no.	Structural formula
SES16470	$C_{14}H_{13}ClN_2O_4S$	340	Lab0006	 (or isomer) [1)]
–	$C_{32}H_{30}Cl_2N_6O_{12}S_2$	824	Lab0008	Oxidative dimer of SES16458
–	–	443	Lab0007	

[1)] Positions of metabolically introduced substituents were not determined.
Source: Thiaener et al. (2012)

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