

KRESOXIM-METHYL

First draft prepared by
D. Kanungo¹ and Ian Dewhurst²

¹ Food Safety and Standards Authority of India, New Delhi, India

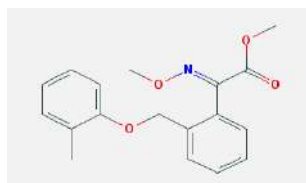
² Sunnycrest, Leavening, North Yorkshire, United Kingdom

Explanation	225
Evaluation for acceptable intake.....	226
1. Biochemical aspects	226
1.1 Absorption, distribution and excretion	226
1.2 Biotransformation	230
2. Toxicological studies.....	233
2.1 Acute toxicity.....	233
2.2 Short-term studies of toxicity.....	234
(a) Oral administration	234
(b) Dermal application.....	238
2.3 Long-term studies of toxicity and carcinogenicity.....	239
2.4 Genotoxicity.....	250
2.5 Reproductive and developmental toxicity.....	252
(a) Multigeneration studies.....	252
(b) Developmental toxicity.....	254
2.6 Special studies.....	255
(a) Neurotoxicity	255
(b) Mechanistic studies on the carcinogenic mode of action.....	256
(c) Other special studies	261
(d) Studies on metabolites	263
3. Observations in humans	264
3.1 Medical surveillance on manufacturing plant personnel.....	264
3.2 Direct observation.....	264
Comments.....	265
Toxicological evaluation.....	269
References	271

Explanation

Kresoxim-methyl (Fig. 1) is the International Organization for Standardization–approved common name for methyl-(*E*)-2-methoxyimino-2-[2-(2-methylphenoxy)methyl]phenyl] acetate (International Union of Pure and Applied Chemistry), with the Chemical Abstracts Service number 143390-89-0.

Fig. 1. Chemical structure of kresoxim-methyl



Kresoxim-methyl is a broad-spectrum fungicide and a member of the strobilurin family, a class of biologically active compounds structurally related to strobilurin A, a natural product of the wood-decaying fungus *Strobilurus tenacellus*. It is intended for use as an agricultural spray in the control and treatment of fungal infections on crops and fruits. Strobilurins are known to bind bcl complex (complex III), one of the oxidoreductase enzymes in the electron transport chain in mitochondria.

Kresoxim-methyl was previously evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1998, when an acceptable daily intake (ADI) of 0–0.4 mg/kg body weight (bw) was established on the basis of a no-observed-adverse-effect level (NOAEL) of 36 mg/kg bw per day in a 24-month study of toxicity and carcinogenicity in rats, with application of a 100-fold safety factor. It was considered to be unnecessary to establish an acute reference dose (ARfD).

Kresoxim-methyl was reviewed by the present Meeting as part of the periodic review programme of the Codex Committee on Pesticide Residues.

Newly submitted studies on acute toxicity, carcinogenicity in a different strain of rat, genotoxicity and neurotoxicity that were not made available to the 1998 Meeting were evaluated by the present Meeting.

All critical studies contained statements of compliance with good laboratory practice (GLP) and were conducted in accordance with relevant national or international test guidelines, unless otherwise specified. No additional information from a literature search was identified that complemented the toxicological information submitted for the current assessment.

Evaluation for acceptable intake

1. Biochemical aspects

1.1 Absorption, distribution and excretion

In a study of biokinetics, kresoxim-methyl labelled with ^{14}C on the phenyl A ring (phenoxy; radiochemical purity >98%) or B ring (phenyl; radiochemical purity >98%) or with ^{13}C on the carbon side-chain was administered to rats (aged about 7–13 weeks at the start of the study) by gavage as a suspension in 0.5% carboxymethylcellulose or intravenously as a 0.9% saline solution.

When groups of five male and five female rats were given [^{14}C -B ring]kresoxim-methyl by gavage at 50 or 500 mg/kg bw, with or without pretreatment with unlabelled kresoxim-methyl, or [^{14}C -A ring]kresoxim-methyl at a dose of 500 mg/kg bw, the compound was excreted predominantly in faeces. At the low dose of [^{14}C -B ring]kresoxim-methyl, faecal excretion represented 65–67% of the administered dose and urinary excretion represented 20–28% of the dose within 48 hours; less than 1% of the radiolabel was recovered in urine and faeces after this time. Pretreatment with unlabelled kresoxim-methyl at the low dose for 14 days did not change the excretion pattern. At the high dose, faecal excretion represented 80–81% of the administered dose and urinary excretion represented 8–13% of the dose within 48 hours. The total radiolabel recovered within 120 hours was 97% of the dose with [^{14}C -A ring]kresoxim-methyl and 90–96% of the dose with [^{14}C -B ring]kresoxim-methyl, with 62–78% of the dose with [^{14}C -A ring]kresoxim-methyl and 81% of the dose with [^{14}C -B ring]kresoxim-methyl excreted in faeces and 17–33% of the dose with [^{14}C -A ring]kresoxim-methyl and 9–13% of the dose with [^{14}C -B ring]kresoxim-methyl excreted in urine. No radiolabel was detected in exhaled air.

In the groups given [^{14}C -B ring]kresoxim-methyl, peak concentrations of radiolabel in plasma were reached 0.5–1 hour after dosing at the low dose and 8 hours after dosing at the high dose. The plasma level then declined, with a terminal half-life of 17–19 hours at the low dose and 22–31 hours at the high dose. The ratios of the area under the plasma concentration–time curve (AUC) for the high:low dose (10:1) were 2.3 for males and 2.1 for females (Table 1).

Radiolabel concentrations were determined in tissues 0.5, 8, 24, 96 and 120 hours after dosing. Except for the gastrointestinal tract, the highest residual concentration was found in the liver (0.1 µg equivalents [Eq]/g at 120 hours and 0.3–1.4 µg Eq/g at 24 hours after dosing at 50 mg/kg bw). The residual concentrations in other tissues were less than 0.1 µg Eq/g tissue at 120 hours after dosing at 50 mg/kg bw. The concentrations of radiolabel in the tissues were comparable in males and females, indicating a similar pattern of wide distribution and subsequent elimination.

Table 1. Pharmacokinetic parameters of radioactivity in plasma after single oral administration of ^{14}C -labelled kresoxim-methyl to male and female rats at 50 or 500 mg/kg bw

Sex	Dose (mg/kg bw)	$C_{\max}$ ($\mu\text{g/g}$)	$T_{\max}$ (h)	Terminal half-life (h)	AUC ($\mu\text{g}\cdot\text{g/h}$)	Total clearance ($\mu\text{g/min}$)
Male	500	3.36	8.0	30.5	85.94	97.0
	50	1.59	1.0	19.1	36.88	22.6
Female	500	3.92	8.0	22.1	76.49	109.0
	50	2.58	0.5	16.9	36.22	23.0

AUC: area under the plasma concentration–time curve; bw: body weight; $C_{\max}$: maximum concentration; $T_{\max}$: time to reach maximum concentration

Source: Gans & Hildebrand (1994)

Groups of five male and five female rats given [^{14}C -B ring]kresoxim-methyl intravenously as a single dose of 5 mg/kg bw excreted 49–66% of the radiolabel in urine and 23–48% in faeces within 120 hours. Faecal excretion was considerably lower after parenteral administration than after ingestion (23–48% versus 80–81%), and the fraction of the dose excreted via the urine was correspondingly increased, indicating incomplete absorption and some excretion into the gastrointestinal tract.

Groups of four male and four female rats with cannulated bile ducts were given the [^{14}C -B ring]-labelled material as a single oral dose of 50 or 500 mg/kg bw. Biliary excretion accounted for 35–43% of the radiolabel at the low dose and 14–15% at the high dose within 48 hours. Excretion of the [^{14}C -A ring]-labelled material in bile was not examined.

If it is assumed that the amount of radioactivity excreted via bile and urine represents the bioavailable amount of ^{14}C -labelled kresoxim-methyl, then absorption rates of 22–28% for the high dose and 55–71% for the low dose can be calculated. Increasing the dose by a factor of 10 resulted in a decrease of absorption rate by a factor of about 2.5 in both sexes, indicating that absorption is saturated at high doses. This result is in agreement with the $C_{\max}$ results obtained from the plasma and blood level experiment, where $C_{\max}$ values increased with dose, but not dose proportionally (Gans & Hildebrand, 1994; Gans, 1995a).

To determine the tissue distribution of radioactivity after a single oral dose at different time points and doses, ^{14}C -labelled kresoxim-methyl (B ring) (lot/batch no. 445-25; chemical purity 97.2%; radiochemical purity 99.2%) was administered to groups of Wistar (Chbb:THOM(SPF)) rats (7 weeks of age at the time of administration; weight at dosing 210–243 g for males and 170–216 g for females) by oral gavage at a single dose of 50 or 500 mg/kg bw. The study was conducted with four sacrifice intervals per dose group. The high-dose group comprised three males and three females per time point, whereas the low-dose group comprised three females per time point only. The sacrifice intervals were based on the plasma toxicokinetics study (Gans & Hildebrand, 1994). In the low-dose group, the time points were $T_{\max} = 0.5$ hour, $1/2 T_{\max} = 8$ hours, $1/4 T_{\max} = 24$ hours and $1/8 T_{\max} = 96$ hours. In the high-dose group, animals were sacrificed at $T_{\max} = 8$ hours, $1/2 T_{\max} = 20$ hours, $1/4 T_{\max} = 24$ hours and $1/8 T_{\max} = 96$ hours. After sacrifice, remaining radioactivity was measured in the following organs of the high-dose group after solubilization: heart, carcass, fat (adipose) tissue, liver, bone, plasma, muscle, spleen, kidney, thyroid glands, gonads, skin, adrenal glands, brain, blood cells, lung, pancreas, bone marrow, intestinal tract and contents, and stomach and stomach contents. In the low-dose group (all females), only ovaries/uterus and bone marrow were analysed.

After oral administration of ^{14}C -labelled kresoxim-methyl at a dose of 500 mg/kg bw to male and female rats, there was a rapid absorption of radioactive material from the gastrointestinal tract. Radioactive material was distributed in all tissues and organs throughout the body (Tables 2 and 3).

Eight hours after administration of radiolabelled kresoxim-methyl to male and female rats, the highest tissue concentrations were found in the contents of the gastrointestinal tract, liver, kidney, adrenal glands and carcass, ranging from 37.50 to 14 090 $\mu\text{g Eq/g}$. In females, the concentration also

exceeded 30 µg Eq/g (30 parts per million [ppm]) in ovary/uterus, adipose tissue and pancreas. The lowest concentrations were measured in bone marrow and brain (0.40–2.52 µg Eq/g). Ninety-six hours after dosing, concentrations of radioactivity were below 50 µg Eq/g (50 ppm) in all organs and tissues. There was no evidence of accumulation of radioactive material after dosing with ¹⁴C-labelled kresoxim-methyl (Tables 2 and 3).

Thirty minutes after oral administration of ¹⁴C-labelled kresoxim-methyl to female rats at a dose of 50 mg/kg bw, there was radioactive material detectable in bone marrow (0.09 µg Eq/g) and in the ovary/uterus (36.88 µg Eq/g). The concentration of radioactivity declined continuously. Ninety-six hours after the administration, the concentration in both tissues was below 0.5 µg Eq/g (0.5 ppm). The results are shown in Table 4.

Table 2. Mean tissue concentrations of radioactivity after single oral administration of ¹⁴C-labelled kresoxim-methyl to rats at a dose of 500 mg/kg bw

Organ/tissue	Mean tissue concentration of radioactivity (µg Eq/g tissue)					
	8 hours		24 hours		96 hours	
	Males	Females	Males	Females	Males	Females
Blood cells	3.33	7.06	2.33	2.56	0.99	1.24
Plasma/serum	22.19	23.68	6.77	4.05	0.91	0.93
Lung	19.18	18.99	7.69	7.93	4.58	4.80
Heart	10.66	11.44	6.36	6.84	4.79	5.89
Spleen	11.92	11.90	10.10	8.66	5.43	7.33
Kidney	57.32	59.23	20.35	10.88	3.05	3.16
Adrenals	53.91	55.07	36.60	36.12	36.15	33.50
Testes	7.95	–	4.22	–	2.63	–
Ovary/uterus	–	55.73	–	62.92	–	37.89
Muscle	24.71	8.53	23.45	21.09	30.03	16.17
Brain	1.46	2.52	0.43	0.32	0.21	0.22
Adipose tissue	12.78	48.76	21.16	17.91	9.61	8.94
Bone	6.62	8.82	6.57	7.39	7.67	5.21
Thyroid	29.72	12.62	10.99	11.90	8.92	10.42
Pancreas	27.96	213.28	43.15	65.18	14.10	11.09
Stomach contents	14 089.94	10 072.14	545.97	203.17	6.43	17.34
Stomach	2 347.85	1 943.42	128.20	104.69	15.66	47.61
Gut contents	5 625.08	6 631.68	590.79	460.74	17.80	16.95
Gut	726.72	681.95	381.89	375.57	24.53	21.47
Liver	58.01	63.33	17.30	13.03	3.85	4.01
Skin	21.81	22.22	14.62	12.23	11.19	7.95
Carcass	37.50	44.91	4.03	3.73	3.68	2.89
Bone marrow	1.67	0.40	0.41	0.32	0.24	0.23

bw: body weight; Eq: equivalents

Source: Gans (1995b)

Table 3. Mean tissue concentrations of radioactivity after single oral administration of ^{14}C -labelled kresoxim-methyl to rats at a dose of 500 mg/kg bw

Organ/tissue	Mean tissue concentration of radioactivity (% of administered dose)					
	8 hours		24 hours		96 hours	
	Males	Females	Males	Females	Males	Females
Blood cells	0.01	0.03	0.01	0.01	0.00	0.00
Plasma/serum	0.09	0.08	0.02	0.01	0.00	0.00
Lung	0.02	0.02	0.01	0.01	0.01	0.01
Heart	0.01	0.01	0.00	0.01	0.00	0.00
Spleen	0.01	0.01	0.01	0.00	0.00	0.00
Kidney	0.09	0.08	0.03	0.02	0.00	0.01
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Testes	0.02	—	0.01	—	0.01	—
Ovary/uterus	—	0.02	—	0.03	—	0.02
Muscle	0.01	0.01	0.01	0.03	0.02	0.01
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.01	0.03	0.01	0.01	0.01	0.01
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.01	0.00	0.00	0.00	0.00	0.00
Pancreas	0.01	0.15	0.02	0.05	0.01	0.01
Stomach contents	31.93	19.93	1.10	0.19	0.02	0.04
Stomach	3.17	2.22	0.28	0.13	0.02	0.05
Gut contents	56.76	64.43	7.11	4.89	0.23	0.17
Gut	4.25	3.41	1.71	1.77	0.14	0.11
Liver	0.58	0.52	0.21	0.15	0.04	0.04
Skin	0.83	0.70	0.50	0.41	0.43	0.25
Carcass	3.43	4.45	0.41	0.40	0.38	0.31
Bone marrow	0.00	0.00	0.00	0.00	0.00	0.00

bw: body weight

Source: Gans (1995b)

Table 4. Mean tissue concentrations of radioactivity after single oral administration of ^{14}C -labelled kresoxim-methyl to female rats at a dose of 50 mg/kg bw

Organ/tissue	Mean tissue concentration of radioactivity							
	0.5 hour		8 hours		24 hours		96 hours	
	$\mu\text{g Eq/g}$	%	$\mu\text{g Eq/g}$	%	$\mu\text{g Eq/g}$	%	$\mu\text{g Eq/g}$	%
Ovary/uterus	36.88	0.21	4.83	0.02	0.91	0.00	0.48	0.00
Bone marrow	0.09	0.00	0.06	0.00	0.03	0.00	0.03	0.00

bw: body weight; Eq: equivalents

Source: Gans (1995b)

In view of the above, it is concluded that after oral administration of ^{14}C -labelled kresoxim-methyl at a dose of 500 mg/kg bw to male and female rats, there was a rapid but incomplete absorption of radioactive material from the gastrointestinal tract. Radioactive material was distributed in all tissues and organs throughout the body, but concentrations of radioactivity were below 50 $\mu\text{g Eq/g}$ (50 ppm) in all organs and tissues at 96 hours after dosing. There was no evidence of accumulation of radioactive material after dosing with kresoxim-methyl, but clearance from several tissues and organs was slow (Table 2).

Thirty minutes after oral administration of ^{14}C -labelled kresoxim-methyl to female rats at a dose of 50 mg/kg bw, there was radioactive material detectable in bone marrow (0.09 $\mu\text{g Eq/g}$) and in the ovary/uterus (36.88 $\mu\text{g Eq/g}$). The concentration of radioactivity declined continuously. At 96 hours after administration, the concentration in both tissues was below 0.5 $\mu\text{g Eq/g}$ (0.5 ppm) (Gans et al., 1995b).

The tissue distribution of radioactivity was determined by quantitative whole body autoradiography following a single oral administration of ^{14}C -labelled kresoxim-methyl (radiochemical purity 96.6%) to male and female albino Crl:(WI) BR rats (approximately 9 weeks of age at the start of administration; weight 207–216 g for males and 161–182 g for females) at a nominal dose of 50 mg/kg bw.

The absorption of ^{14}C -labelled kresoxim-methyl-derived material was low, and uptake into the tissues was limited. Other than the gastrointestinal tract, the highest concentrations of radioactivity were associated with the organs of metabolism and elimination (i.e. liver and kidney). As most of the administered radioactivity was confined to the gastrointestinal tract, lower concentrations were found in liver (5.269 and 4.939 $\mu\text{g Eq/g}$ at 0.5 and 2 hours, respectively) and kidney (6.483 and 6.514 $\mu\text{g Eq/g}$, respectively). Of the remaining tissues where radioactivity was present (i.e. blood, bone marrow, brain, eye [including uveal tract], Harderian gland, lung, muscle [including myocardium], salivary glands, gonads [male rats], thymus and thyroid), ^{14}C -labelled kresoxim-methyl concentrations were below 1.6 $\mu\text{g Eq/g}$ tissue. At 24 hours post-dosing, radioactivity was detected only in the contents of the gastrointestinal tract (at moderate levels) and in the liver and skin (at low levels). After 96 hours, radioactivity persisted at low levels in the contents of the gastrointestinal tract in both sexes, as well as in or on the skin of the females (Whitby, 1993).

1.2 Biotransformation

The samples collected in the experiments described above (Gans & Hildebrand, 1994) were analysed for metabolites of kresoxim-methyl. After oral administration, high proportions of parent compound were found in the faeces, but none was detected in the bile or in tissues (plasma, liver and kidney) sampled about 4 hours after administration of the low or high dose (Tables 5 and 6).

In total, 34 metabolites, including conjugates, were identified by nuclear magnetic resonance spectroscopy and mass spectrometry in rat excreta, with 20 in urine, eight in faeces and 17 in bile. The major metabolites identified in urine and faeces were M1, a hydrolytic product of the acetyl ester; M2, an oxidative metabolite of the aryl-methyl moiety of M1; and M9, a hydroxylated metabolite of the phenoxy ring of M1. M1 and M9 were the major metabolites identified in tissues. Glucuronidated conjugates were detected in notable quantities in the bile. There was no evidence that the metabolic pathways were induced by pretreatment with kresoxim-methyl. A small difference in the metabolite pattern in urine and bile was observed between males and females, the percentages of M1 and M9 in urine from females being greater than in urine from males.

In summary, the metabolic pathways of kresoxim-methyl consisted of hydrolytic cleavages of the ester, the oxime ether and the benzyl ether bonds; hydroxylation at the *para* position of the phenoxy ring; oxidation of the aryl-methyl group to benzyl alcohol and its subsequent oxidation to the corresponding carboxylic acid; and conjugation of the resulting hydroxy groups with glucuronate and sulfate (Kohl, 1994, 1995, 1998; Annex 1, reference 85).

Table 5. Presence of parent compound and metabolites in excreta following administration of a single oral dose of ^{14}C -labelled kresoxim-methyl to rats

Substance	Concentration (% of administered dose)							
	Faeces				Urine			
	50 mg/kg bw		500 mg/kg bw		50 mg/kg bw		500 mg/kg bw	
	Males	Females	Males	Females	Males	Females	Males	Females
Parent	49.5	47.1	74.9	39.5	–	–	–	–
M1	2.1	–	0.1	7.1	0.4	2.7	2.8	2.2
M2	2.7	0.5	0.5	5.8	2.0	3.4	1.5	2.0
M4	1.1	0.5	0.3	2.5	Mix1	Mix1	Mix1	Mix1
M6	–	–	–	–	2.8	1.1	1.9	0.5
M8	–	–	–	–	0.1	0.4	–	Mix3
M9	5.2	6.0	0.9	13.3	5.5	11.0	2.7	4.9
M11	–	–	–	–	Mix2	–	Mix2	Mix3
M12	–	–	–	–	Mix2	–	Mix2	Mix3
M14	–	–	–	–	Mix1	Mix1	Mix1	Mix1
M15	1.3	2.7	0.1	3.4	–	–	–	–
M16	–	–	–	–	–	–	0.3	Mix3
M20	–	–	–	–	Mix1	Mix1	Mix1	Mix1
M24	–	–	0.1	–	–	–	0.1	0.4
M26	–	–	–	–	Mix2	–	Mix2	Mix3
Mix1	–	–	–	–	1.4	1.6	0.9	1.1
Mix2	–	–	–	–	0.9	–	0.8	–
Mix3	–	–	–	–	–	–	–	1.4
UK1	1.3	0.6	0.4	0.1	–	0.1	–	0.2
UK2	–	0.2	0.1	1.4	–	–	–	–
UK3	–	–	0.1	1.8	–	–	–	–
UK4	–	–	0.3	–	–	–	–	–
UK5	–	–	0.2	–	–	–	–	–
UK6	–	–	–	0.1	–	–	–	–

bw: body weight; Mix1: mixture of M4 + M14 + M20; Mix2: mixture of M11 + M12 + M26; Mix3: mixture of M8 + M11 + M12 + M26; UK: unknown compound

Source: Annex 1, reference 85

Table 6. Presence of parent compound and metabolites in bile and tissues following administration of a single oral dose of ^{14}C -labelled kresoxim-methyl to rats^a

Substance	Concentration (% of administered dose) ^b							
	Bile		Plasma		Liver			
	50 mg/kg bw		50 mg/kg bw		50 mg/kg bw		500 mg/kg bw	
	Males	Females	Males	Females	Males	Females	Males	Females
Parent	0	0	0	0	0	0	0	0
M1	1.7	1.9	0.386	0.304	0.13	0.07	0.07	0.12
M2	Mix5	Mix5	0.095	Mix8	0.08	0.04	0.04	0.04
M4	–	–	0.041	Mix8	0.03	0.02	0.04	0.02
M6	–	–	0.027	0.006	–	–	–	–
M9	1.1	1.3	0.173	0.164	0.17	0.07	0.06	0.09
M11	–	–	0.002	–	Mix4	Mix4	Mix4	Mix4

Substance	Concentration (% of administered dose) ^b							
	Bile		Plasma		Liver			
	50 mg/kg bw		50 mg/kg bw		50 mg/kg bw		500 mg/kg bw	
	Males	Females	Males	Females	Males	Females	Males	Females
M28	0.7	2.9	—	—	—	—	—	—
M31	0.5	1.1	—	—	—	—	—	—
M35	1.7	0.7	—	—	—	—	—	—
M44	0.4	0.3	—	—	—	—	—	—
M45	Mix5	Mix5	—	—	—	—	—	—
Mix4	—	—	0.115	—	0.08	0.02	0.02	0.01
Mix5	1.1	1.2	—	—	—	—	—	—
Mix6	6.3	3.6	—	—	—	—	—	—
Mix7	0.4	0.2	—	—	—	—	—	—
Mix8	—	—	—	0.169	—	—	—	—
UK1	—	—	—	—	0.02	—	—	—
UK2	—	—	—	0.024	0.02	0.01	—	—

bw: body weight; Mix4: mixture of M11 + M12 + M16 + M34 + M36 + M37; Mix5: mixture of M2 + M45; Mix6: mixture of M25 + M26 + M29 + M33 + M39; Mix7: mixture of M34 + M36 + M37; Mix8: mixture of M2 + M4; UK: unknown compound

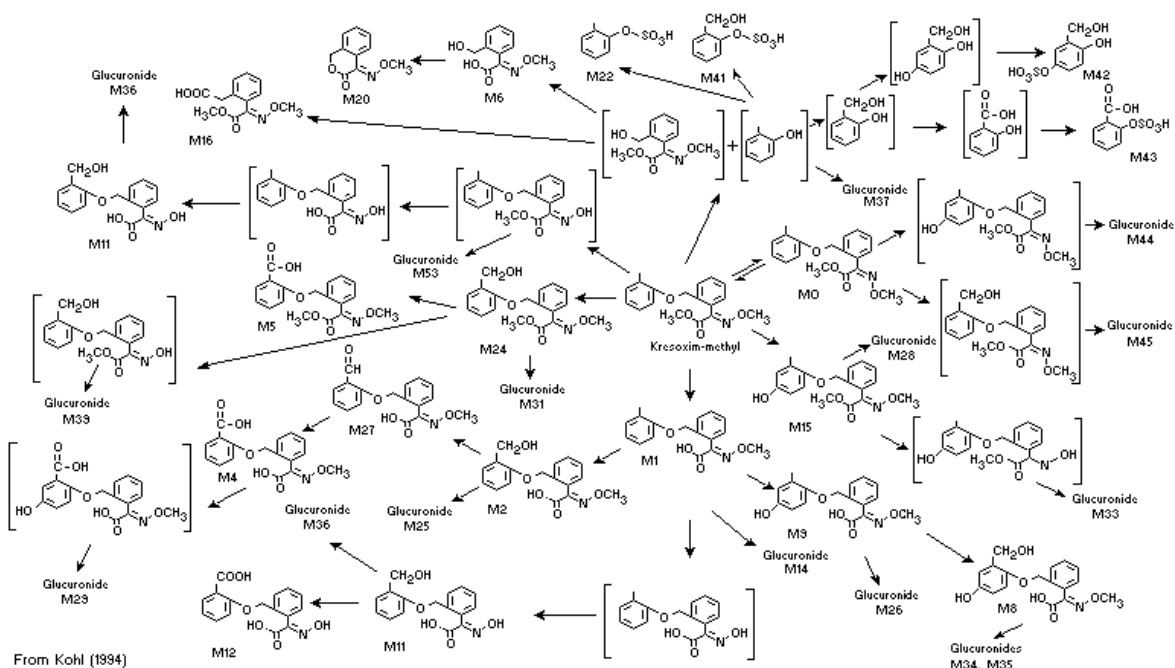
^a The tissue samples were collected 3.5–4 hours after single-dose administration.

^b The values in plasma are expressed as microgram equivalents per millilitre.

Source: Annex 1, reference 85

The proposed metabolic pathway for kresoxim-methyl in rats is shown in Fig. 2.

Fig. 2. Metabolic pathway of kresoxim-methyl in rats



Source: Kohl (1994)

2. Toxicological studies

2.1 Acute toxicity

Several studies found kresoxim-methyl to have low acute toxicity when administered orally, dermally or through inhalation to rats (Table 7).

Table 7. Summary of acute toxicity studies with kresoxim-methyl

Species	Strain	Sex	Route	Purity (%)	LD ₅₀ (mg/kg bw) / LC ₅₀ (mg/L air)	Reference
Mouse	ICR	M + F	Oral	94.3	>5 000	Yamamoto (1994)
Rat	Chbb Wistar	M + F	Oral	93.7	>5 000	Kirsch & Hildebrand (1993a)
Rat	Wistar / CrI:WI (Han)	F	Oral	86.4	>2 000	Cords & Lammer (2011a)
Rat	Chbb Wistar	M + F	Dermal	93.7	>2 000	Kirsch & Hildebrand (1993b)
Rat	Wistar / CrI:WI (Han) SPF	M + F	Dermal	86.4	>2 000	Cords & Lammer (2011b)
Rat	Chbb Wistar	M + F	Inhalation	96.6	>5.6 (MMADs of 1.8–2.4 µm)	Gamer (1992)
Rat	Wistar / RccHan:WIST	M + F	Inhalation	86.4	>5.263 (MMADs of 4.1 and 4.0 µm)	Wittmer & Landsiedel (2011)

bw: body weight; F: female; LC₅₀: median lethal concentration; LD₅₀: median lethal dose; M: male; MMAD: mass median aerodynamic diameter

None of the studies included in Table 7 reported any death or abnormal clinical signs in mice or rats, and no abnormal changes in organs were seen at necropsy.

Kresoxim-methyl was not irritating to the skin or to the eyes of rabbits. It was also not sensitizing to the skin of guinea-pigs (Table 8).

Table 8. Summary of dermal and eye irritation and skin sensitization studies with kresoxim-methyl

Species	Strain	Sex	End-point	Purity (%)	Result	Reference
Rabbit	White Vienna	NS	Skin irritation	NS	Not irritating	Rosbacher (1992a)
Rabbit	New Zealand white CrI:KBL (NZW) SPF	F	Skin irritation	86.4	Not irritating	Wolf (2011a)
Rabbit	White Vienna	NS	Eye irritation	NS	Not irritating	Rosbacher (1992b)
Rabbit	New Zealand white	F	Eye irritation	86.4	Not irritating	Wolf (2011b)

Species	Strain	Sex	End-point	Purity (%)	Result	Reference
Guinea-pig	CrI:KBL (NZW) SPF					
	Dunkin Hartley HOE DHPK	NS	Skin sensitization	NS	Not sensitizing (Magnusson & Kligman test)	Rossbacher (1993)
Guinea-pig	Hartley CrI:HA	F	Skin sensitization	86.4	Not sensitizing (Buehler test)	Weiss-Fuchs (2011)

bw: body weight; F: female; NS: not specified

2.2 Short-term studies of toxicity

(a) Oral administration

Short-term studies of oral toxicity in mice, rats and dogs were conducted.

Mice

In a 28-day range-finding study, groups of five male and five female B6C3F1(Cr) mice (aged 49 days at the start of the study; mean body weight 24 g [23–25 g] for males and 19 g [18–20 g] for females) were given diets containing kresoxim-methyl (purity 96.6%) at a concentration of 0, 500, 2000 or 8000 parts per million (ppm) (equal to 0, 113, 485 and 2141 mg/kg bw per day for males and 0, 182, 798 and 3755 mg/kg bw per day for females, respectively). The animals were observed for clinical signs, death, feed consumption, body weight and clinical chemical, haematological and pathological end-points.

There were no deaths or signs of clinical toxicity. At the high dose, significantly reduced serum concentrations of triglycerides, cholesterol and lymphocytes were observed in males, and significantly increased relative liver weights (males: 13%; females: 12%) ($P < 0.01$) (Table 9) without any associated histopathological changes were observed in animals of both sexes. No compound-related lesions were observed on histopathological examination.

Table 9. Body weight and liver weights in mice administered kresoxim-methyl for 28 days

Parameter		Males				Females			
		0 ppm	500 ppm	2 000 ppm	8 000 ppm	0 ppm	500 ppm	2 000 ppm	8 000 ppm
Body weight	Mean	24.48	24.50	24.84	22.78	18.54	18.44	18.14	18.78
	(g)	–	(+0.08) ^a	(+1.47)	(–6.9)	–	(–0.54)	(–2.15)	(+1.29)
Absolute liver weight	Mean	1.1	1.072	1.141	1.156	0.902	0.854	0.941	1.021
	(g)	–	(–2.5)	(+3.72)	(+5.1)	–	(–5.3)	(+4.3)	(+13.2)
Relative liver weight	Mean	4.489	4.378	4.598	5.071**	4.857	4.627	5.186	5.434**
	(%)	–	(–2.5)	(+2.4)	(+13)	–	(–5)	(+7)	(+12)

ppm: parts per million; **: $P < 0.01$ (Kruskal-Wallis H test + Wilcoxon test)

^a Per cent change relative to controls given in parentheses.

Source: Schilling & Hildebrand (1992a)

The NOAEL was 8000 ppm (equal to 2141 mg/kg bw per day), the highest dose tested (Schilling & Hildebrand, 1992a).

In a 3-month study, groups of 10 male and 10 female C57Bl/6N(Cr) mice (aged 55 days at the start of the study; mean body weight 22 g [20–24 g] for males and 18 g [17–19 g] for females) were given diets containing kresoxim-methyl (purity 98.7%) at a concentration of 0, 250, 1000, 4000 or 8000 ppm (equal to 0, 57, 230, 909 and 1937 mg/kg bw per day for males and 0, 80, 326, 1326 and 2583 mg/kg bw per day for females, respectively). The animals were observed for clinical signs, death, feed consumption, body weight, clinical chemistry parameters, including the activities of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), and haematological and pathological end-points.

There were no deaths, signs of clinical toxicity or changes in haematological or clinical chemistry parameters. Dose-dependent reductions in terminal body weight, by 4.0% at 4000 ppm and 7.1% at 8000 ppm, and body weight gain, by 11% at 4000 ppm and 24% at 8000 ppm, were seen in males. Statistically significant increases in relative liver weight were observed in males at 4000 ppm (10.6%) and 8000 ppm (18.9%), without any associated compound-related histopathological changes (Table 10).

Table 10. Body weight and liver weights in mice administered kresoxim-methyl for 3 months

		Males					Females				
Parameter		0 ppm	250 ppm	1 000 ppm	4 000 ppm	8 000 ppm	0 ppm	250 ppm	1 000 ppm	4 000 ppm	8 000 ppm
Body weight	Mean (g)	30.9	30.4	31.3	29.7	28.7	23.6	23.5	23.2	23.7	24.3
		–	(–1.6)	(+3.3)	(–4.0)	(–7.1)	–	(–0.4)	(–1.7)	(+0.4)	(+3.0)
Body weight gain	%	–	–3.2	+6.5	–11	–24	–	–5	–15	–10	+1.6
Absolute liver weight	Mean (g)	1.141	1.173	1.168	1.178	1.219	0.953	0.927	0.938	1.017	1.018
		–	(+2.8)	(+2.4)	(+3.2)	(+6.8)	–	(–2.7)	(–1.6)	(+6.7)	(+6.8)
Relative liver weight	Mean (%)	4.396	4.645	4.514	4.866	5.227	5.026	4.886	5.05	5.308	5.361
		–	(+5.6)	(+2.6)	(+10.6)**	(+18.9)**	–	(–2.8)	(+0.5)	(+5.6)	(+6.7)

ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$ (Dunnett test, two-sided)

^a Per cent change relative to controls given in parentheses.

Source: Mellert & Hildebrand (1994a,b)

The NOAEL was 1000 ppm (equal to 230 mg/kg bw per day), based on decreases in body weight gain (>10%) in males at 4000 ppm (equal to 909 mg/kg bw per day) (Mellert & Hildebrand, 1994a,b).

Rats

In a 28-day range-finding study, groups of five male and five female Wistar (Cr) rats (Chbb:Thom(SPF); aged 42 days at the start of the study; mean body weight 178 g for males and 142 g for females) were given diets containing kresoxim-methyl (purity 96.55%) at a concentration of 0, 1000, 4000 or 16 000 ppm (equal to 0, 91, 365 and 1428 mg/kg bw per day for males and 0, 95, 375 and 1481 mg/kg bw per day for females, respectively). The rats were observed for clinical signs, death, feed consumption, body weight, clinical chemistry parameters, including the activities of serum ALT, AST, ALP and GGT, and haematological and pathological end-points.

There were no deaths, signs of clinical toxicity or changes in haematological parameters. The terminal body weights were slightly reduced in animals of both sexes at 4000 ppm (by 4% in males and

10% in females) and at 16 000 ppm (by 7% in males and 6% in females), and the absolute liver weights were slightly increased in males (by 8%) and females (9%) at 16 000 ppm; however, these changes were not statistically significant. Statistically significant increases in relative liver weights (18%) were observed in females at 16 000 ppm, and statistically significantly increased serum GGT activity and albumin concentration were observed in males at this dose. No compound-related lesions were observed on histopathological examination. There were no clear substance-related effects on thyroid stimulating hormone (TSH), triiodothyronine (T₃) or thyroxine (T₄).

The NOAEL was 4000 ppm (equal to 365 mg/kg bw per day), based on the increased serum GGT activity in males, increased albumin concentration in males and increased relative liver weight in females at 16 000 ppm (equal to 1428 mg/kg bw per day) (Schilling & Hildebrand, 1992b).

In a 90-day study, groups of 10 male and 10 female Wistar (Cr) rats (Chbb:Thom(SPF); aged 42 days at the start of the study; mean body weight 182 g for males and 141 g for females) were given diets containing kresoxim-methyl (purity 98.7%) at a concentration of 0, 500, 2000, 8000 or 16 000 ppm (equal to 0, 36, 146, 577 and 1170 mg/kg bw per day for males and 0, 43, 172, 672 and 1374 mg/kg bw per day for females, respectively). The rats were observed for clinical signs, death, feed consumption, body weight, clinical chemistry parameters, including the activities of serum ALT, AST, ALP and GGT, and haematological and pathological end-points. Feed consumption and body weight were determined once a week, and enzyme activities were determined after 6 weeks and at the end of the study.

There were no deaths, signs of clinical toxicity, changes in feed consumption or any compound-related changes in haematological parameters.

Slight but statistically significant decreases in terminal body weight (7–8% at 8000 ppm and 11–13% at 16 000 ppm) and body weight gain (7–10% at 8000 ppm and 13–15% at 16 000 ppm) were observed in males. Statistically significant increases in relative liver weight were observed in males at 16 000 ppm (10%) and in females at 2000 ppm and higher (10% at 2000 ppm, 7% at 8000 ppm and 12% at 16 000 ppm). Statistically significant increases in relative kidney weight were also observed in males, but the absolute weights were not increased. No compound-related histopathological lesions were observed in these or other organs in treated groups. Dose-dependent, statistically significantly increased activities of GGT were observed in males at 8000 ppm and higher, and statistically significantly decreased activities of ALP and ALT were observed in males at all doses and in females at 2000 ppm and higher. These reductions in enzyme activity were considered to be related to the slight decrease in feed consumption on the basis of a mechanistic study (Moss, 1994) on per cent reductions in intestinal and hepatic isozymes per total serum ALP activity (see section 2.6(c) below).

The NOAEL was 2000 ppm (equal to 146 mg/kg bw per day), based on decreased body weight and body weight gain and increased GGT activity in males at 8000 ppm (equal to 577 mg/kg bw per day) (Mellert & Hildebrand, 1994c).

Dogs

In a 3-month study, groups of six male and six female beagles (6–9 months old; mean body weights 11.3 kg [8.2–13.7 kg] for males and 9.8 kg [7.9–12.6 kg] for females) were given diets containing kresoxim-methyl (purity 94–95.9%) at a concentration of 0, 1000, 5000 or 25 000 ppm (equal to 0, 30, 150 and 776 mg/kg bw per day for males and 0, 34, 168 and 846 mg/kg bw per day for females, respectively). The animals were observed for clinical signs, death, feed consumption, body weight, clinical chemistry parameters, including the activities of serum ALT, AST, ALP and GGT, and haematological and pathological end-points. Blood samples for haematological and clinical chemistry analysis were collected prior to treatment (day –3) and during weeks 4 and 13 of treatment.

No deaths or ophthalmological abnormalities were observed. During the first 3 weeks, diarrhoea and vomiting were observed frequently in most animals at 25 000 ppm, and a slight but statistically significant reduction in body weight gain was observed in females at this dose throughout

the study. There were no treatment-related changes in haematological or urinary parameters; slight but statistically significant decreases in the concentration of total protein were observed in males at 25 000 ppm, and statistically significant decreases in the concentration of albumin were observed in females at 5000 ppm and in both sexes at 25 000 ppm. These changes were observed during week 4 of treatment but had disappeared by week 13. The changes in albumin and total protein concentrations might not be related to treatment, because they were slight, were transient and may have been a result of the vomiting and diarrhoea that occurred during the first weeks of the study. Dose-dependent increases in the absolute and relative weights of the liver were observed, but were not statistically significant. Histopathological examination revealed no compound-related lesions in tissues, including the liver.

The NOAEL was 5000 ppm (equal to 150 mg/kg bw per day), on the basis of vomiting and diarrhoea in animals of both sexes and reduced body weight gain in females at 25 000 ppm (equal to 776 mg/kg bw per day) (Mellert & Hildebrand, 1994d).

In a 12-month study, groups of six male and six female beagles (6–8 months old; mean body weight 11.0 kg [7.3–13.2 kg] for males and 9.9 kg [8.0–11.5 kg] for females) were given diets containing kresoxim-methyl (purity 93.7%) at a concentration of 0, 1000, 5000 or 25 000 ppm (equal to 0, 27, 140 and 710 mg/kg bw per day for males and 0, 30, 150 and 760 mg/kg bw per day for females, respectively). The animals were observed for clinical signs, death, feed consumption, body weight, ophthalmological end-points, clinical chemistry parameters, including the activities of serum ALT, AST, ALP and GGT, haematological parameters, including clotting time, and pathological end-points. Blood samples were collected for haematological and clotting analysis and clinical chemistry after 3, 6 and 12 months of treatment.

No deaths or ophthalmological abnormalities were observed. Diarrhoea and vomiting occurred infrequently in animals of both sexes at 25 000 ppm, and the body weights of males at this dose were statistically significantly reduced at study termination. The mean body weight of the test group males at 25 000 ppm was statistically significantly reduced from day 189, resulting in about a 12% reduction in body weight at the end of the study in comparison with the concurrent controls. The finding was predominantly caused by one male dog (No. 19.2), which had a 10% reduction in body weight, leading to an overall mean reduction of body weight gain. The details are shown in Tables 11, 12 and 13.

Table 11. Body weight and body weight changes of beagles during the study administration period

Dietary concentration (ppm)	Sex	Body weight (kg)				Body weight change during administration (day 0 vs day 364)	
		Day 0	Day 91	Day 182	Day 364	Mean (kg)	Increase (%) ^a
0	M	10.8	12.5	13.5	14.1	3.3	31
	F	10.0	10.9	11.5	12.2	2.2	22
1 000	M	11.2	12.3	13.1	13.7	2.5	22
	F	10.1	11.0	11.8	12.3	2.2	22
5 000	M	10.9	12.1	12.9	13.4	2.5	23
	F	10.0	11.2	12.0	12.4	2.4	24
25 000	M	11.2	11.8	12.5	12.5	1.3	12
	F	9.7	10.7	11.7	12.4	2.7	28

F: female; M: male; ppm: parts per million

^a Percentage of body weight change relative to body weight at day 0.

Source: Hellwig & Hildebrand (1994)

Table 12. Body weight and body weight changes of individual male dogs at 25 000 ppm

Animal no.	Body weight (kg) on day 0	Body weight (kg) on day 364	% change
19:2	12.7	11.4	-10
23:2	10.6	13.0	22
37:2	12.2	12.7	4
53:2	10.8	12.6	17
59:2	9.5	12.9	36
Mean	11.2	12.5	12

Source: Hellwig & Hildebrand (1994)

Table 13. Body weight and body weight changes of individual male dogs in the control group

Animal no.	Body weight (kg) on day 0	Body weight (kg) on day 364	% change
27:2	13.2	13.8	4.5
39:2	11.7	14.7	26
43:2	11.1	14.8	33
47:2	10.7	13.2	23
65:2	7.3	14.1	93
Mean	10.8	14.1	35.9

Source: Hellwig & Hildebrand (1994)

There was no statistically significant reduction in body weight gain or feed consumption at any dose. Significant increases in the number of platelets were observed in males at all doses; the values for males at 25 000 ppm were within the range of historical control data, except for the mean value at the third month. There were no compound-related changes in clotting time. There were no compound-related changes in urinary or clinical chemistry parameters or in the activities of serum enzymes. Significant increases in relative liver weights were observed in males at 5000 ppm, but the absolute liver weights were not significantly increased. Histopathological examination revealed no treatment-related alterations in the liver or in any other tissue or organ examined.

In view of the above, the NOAEL was 5000 ppm (equal to 140 mg/kg bw per day), based on infrequent diarrhoea and vomiting occurring in animals of both sexes and the significantly reduced body weights of males at study termination at 25 000 ppm (equal to 710 mg/kg bw per day) (Hellwig & Hildebrand, 1994).

(b) Dermal application

Rats

Groups of five male and five female Wistar (Chbb) rats (aged about 8–10 weeks; body weight 200–300 g) received dermal applications of kresoxim-methyl (purity 94.3%) suspended in 0.5% carboxymethylcellulose at a dose of 0 or 1000 mg/kg bw per day under a semi-occlusive dressing (four layers of absorbent gauze and an elastic dressing) for 6 hours per day for 21 days. The rats were observed for clinical signs, death, feed consumption, body weight, clinical chemistry parameters, including the activities of serum ALT, AST, ALP and GGT, haematological parameters, including clotting times, and pathological end-points. Blood samples for haematological and clotting analysis and for clinical chemistry were collected at termination.

There were no compound-related effects on mortality rates, clinical signs, haematological parameters, clotting times or clinical chemistry parameters, including serum enzyme activities. There were no statistically significant changes in body weight gain or feed consumption in the treated group, and no signs of irritation were observed on treated skin of test or control animals. No effect on organ weights was observed, and histopathological examination revealed no treatment-related alterations in the liver or in any other tissue or organ examined.

The NOAEL was 1000 mg/kg bw per day, the highest dose tested (Kirsch & Hildebrand, 1994a).

2.3 Long-term studies of toxicity and carcinogenicity

Mice

In an 18-month study, groups of 50 male and 50 female C57Bl/6N (CrIbR) mice were given diets containing kresoxim-methyl (mean purity 96.3% during the first 12 months and 93.2% during the following 6 months) at a concentration of 0, 400, 2000 or 8000 ppm (equal to 0, 60, 304 and 1305 mg/kg bw per day for males and 0, 81, 400 and 1662 mg/kg bw per day for females, respectively). Satellite groups of 10 mice of each sex were treated concurrently for 12 months. The age of mice at the initiation of administration was 40–50 days, and the groups had a mean weight of 23.3 g (21.1–26.8 g) for males of the main group; 22.9 g (21.0–25.0 g) for males of the satellite group; 18.9 g (17.2–21.2 g) for females of the main group; and 18.8 g (16.9–20.7 g) for females of the satellite group. The animals were observed for clinical signs, death, feed consumption, body weight, and haematological and pathological end-points. Blood samples for haematology were collected during months 12 and 18 of treatment.

No compound-related effects were observed with respect to mortality rates, clinical signs, feed consumption or haematological parameters throughout the study. Survival rates at termination were 86%, 88%, 84% and 82% for males and 80%, 88%, 82% and 84% for females at 0, 400, 2000 and 8000 ppm, respectively. Statistically significant decreases in terminal body weights and body weight gains were observed in the main groups of males at 8000 ppm and females at 2000 and 8000 ppm during the final 6 months (Table 14).

Table 14. Body weight changes of mice receiving kresoxim-methyl in the diet for 18 months

Dietary concentration (ppm)	Body weight (g) ^a							
	Main group				Satellite group			
	Males		Females		Males		Females	
	Day 0	Day 546	Day 0	Day 546	Day 0	Day 371	Day 0	Day 371
0	23.4	39.3	19.1	36.9	23	41.5	19.1	37.7
	–	(68%)	–	(93%)	–	(80%)	–	(97%)
400	23.3	38.6	19.0	36.0	23	40.8	18.9	37.6
	–	(66%)	–	(89%)	–	(77%)	–	(99%)
2 000	23.3	39.0	18.7*	32.7**	22.6	40.9	18.7	36.5
	–	(67%)	–	(75%)	–	(81%)	–	(95%)
8 000	23.2	35.7*	18.8	29.7**	22.8	37.1	18.6	33.6
	–	(54%)	–	(58%)	–	(63%)	–	(81%)

ppm: parts per million; *: $P \leq 0.05$; **: $P \leq 0.01$ (analysis of variance + Dunnett's test, two-sided)

^a Per cent change relative to day 0 given in parentheses.

Source: Mellert & Hildebrand (1994e)

Increased relative liver weights were observed in females in the satellite group examined at 12 months and in the main group examined at 18 months at 8000 ppm (Tables 15 and 16). Increased relative adrenal weights were observed in males at 12 and 18 months and in females at 18 months at 8000 ppm.

Table 15. Mean body weight and liver weights after 52 weeks (day 364)

Parameter		Males				Females			
		0 ppm	400 ppm	2 000 ppm	8 000 ppm	0 ppm	400 ppm	2 000 ppm	8 000 ppm
Body weight	Mean (g)	39.4	38.3	38.3	35.29	33.5	33.27	32.1	29.7
Absolute liver weight	Mean (g)	1.7	1.6	1.7	1.8	1.4	1.4	1.4	1.5
Relative liver weight	Mean (%)	4.4	4.1	4.5	5.0	4.1	4.3	4.6	5.1**

ppm: parts per million; **: $P < 0.01$ (Dunnett's test, two-sided)

Source: Mellert & Hildebrand (1994e)

Table 16. Mean body weight and liver weights after 78 weeks (day 546)

Parameter		Males				Females			
		0 ppm	400 ppm	2 000 ppm	8 000 ppm	0 ppm	400 ppm	2 000 ppm	8 000 ppm
Body weight	Mean (g)	35.0	34.6	34.8	31.9*	33.6	33.6	31.1	27.9**
Absolute liver weight	Mean (g)	1.61	1.66	1.55	1.6	1.6	1.5	1.5	1.6
Relative liver weight	Mean (%)	4.6	4.8	4.5	5.1	4.8	4.6	5.1	5.8**

ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$ (Dunnett's test, two-sided)

Source: Mellert & Hildebrand (1994e)

Histopathological examination at 12 months revealed no compound-related lesions in any group, but examination at 18 months revealed an increased incidence of centrilobular fatty infiltration (1/50 at 0 ppm and 8/50 at 8000 ppm) in the liver in females, an increased incidence and a greater degree of severity of hepatic amyloidosis (6/50 at 0 ppm and 16/50 at 8000 ppm) in females (Table 17) and an increased incidence of papillary necrosis of the kidney (2/50 at 0 ppm and 13/50 at 8000 ppm) in females. There was no treatment-related increase in the incidence of neoplastic lesions.

Table 17. Incidence of non-neoplastic findings in the liver of rats after 78 weeks

Finding	Incidence of finding							
	Males				Females			
	0 ppm	400 ppm	2 000 ppm	8 000 ppm	0 ppm	400 ppm	2 000 ppm	8 000 ppm
No. of livers examined	50	50	50	50	50	50	50	50
Lymphoid infiltration	34	33	36	33	37	40	35	38
Haematopoiesis	4	0	1	1	4	1	0	2

Finding	Incidence of finding							
	Males				Females			
	0 ppm	400 ppm	2 000 ppm	8 000 ppm	0 ppm	400 ppm	2 000 ppm	8 000 ppm
Pigment storage	0	0	0	0	0	1	1	2
Focal fatty infiltration	4	1	2	7	4	2	1	2
Fatty infiltration centrilobular	6	5	2	3	1	2	4	8
Fatty infiltration diffuse	31	33	40	39	40	43	35	33
Amyloidosis	13	11	7	20	6	1	4	16
Storage, Kupffer's cells	0	1	1	0	0	0	0	0
Single-cell necrosis	0	0	0	1	0	0	0	0
Necrosis focal	3	4	3	6	5	0	3	2
Bile duct proliferation	0	1	0	0	0	1	1	0

ppm: parts per million

Source: Mellert & Hildebrand (1994e)

The NOAEL for toxicity was 2000 ppm (equal to 304 mg/kg bw per day), on the basis of reductions in body weight and body weight gain in both sexes and histopathological changes in the liver and increased liver weights in females at 8000 ppm (equal to 1305 mg/kg bw per day). The compound was not carcinogenic up to the highest dose tested (8000 ppm, equal to 1305 mg/kg bw per day) (Mellert & Hildebrand, 1994e).

Rats

In a 24-month toxicity study, groups of 20 male and 20 female Wistar (Chbb:THOM(SPF)) rats (aged 42 days; mean body weights 196 g for males and 147 g for females) were given diets containing kresoxim-methyl (purity 92.7–96.6%) at a concentration of 0, 200, 800, 8000 or 16 000 ppm (equal to 0, 9, 36, 370 and 746 mg/kg bw per day for males and 0, 12, 48, 503 and 985 mg/kg bw per day for females, respectively). The animals were observed for clinical signs, death, feed consumption, body weight, ophthalmological end-points, clinical chemistry parameters, including the activities of serum ALT, AST, ALP and GGT, and haematological, urinary and histopathological end-points. Blood samples for haematology and clinical chemistry were collected at 3, 6, 12, 18 and 24 months of treatment.

There were no treatment-related effects on mortality rates, clinical signs or ophthalmoscopic parameters. The survival rates of males until day 735 were 85%, 40%, 75%, 80% and 80% at 0, 200, 800, 8000 and 16 000 ppm, respectively. In females, the survival rates until day 375 were 75%, 75%, 60%, 80% and 85% at 0, 200, 800, 8000 and 16 000 ppm, respectively. The terminal body weights were slightly reduced in males at 16 000 ppm (by 4%) and statistically significantly reduced in females at 8000 ppm (by 13%) and 16 000 ppm (by 6%). Body weight gains were reduced in males (10% below controls) and females (15% below controls) at both 8000 and 16 000 ppm. No statistically significant change in feed consumption was observed. Slight but statistically significant reductions in mean corpuscular volume and mean corpuscular haemoglobin were observed in males at 16 000 ppm and in females at and above 200 ppm; however, these changes were within the background range and were not clearly dose dependent. The activity of serum ALT was statistically significantly decreased in animals

of both sexes at 8000 and 16 000 ppm, and that of serum ALP was statistically significantly decreased in animals of both sexes at and above 200 ppm. These reductions in enzyme activities are not toxicologically relevant (Moss, 1994; Mellert, Decardt & Hildebrand, 1997). The relative liver weights were statistically significantly increased in males at 8000 and 16 000 ppm, and the absolute liver weights were statistically significantly increased in males at the highest dose. Statistically significant, dose-related increases in GGT activity were also observed in males at and above 8000 ppm.

Microscopic examination revealed evidence of neoplasia in the liver. Increased incidences of hepatocellular carcinoma, but not hepatocellular adenoma, were observed in animals. The incidences are given in Table 18.

Table 18. Incidence of neoplastic and non-neoplastic findings in a 24-month toxicity study in rats (original report)

Finding	Incidence of finding									
	Males					Females				
	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm
No. of animals examined	20	20	20	20	20	20	20	20	20	20
Liver										
Adenoma, hepatocellular	0	0	0	0	0	0	0	0	0	0
Carcinoma, hepatocellular (<i>one-sided P-value</i>)	0	1 (NS)	1 (NS)	3 (NS)	8 (**)	1	0 (NS)	2 (NS)	6* (NS)	6* (NS)
<i>Chi-squared analysis</i>		0.00	0.00	1.41	7.46		0.00	0.00	2.70	2.70
Hepatocellular hypertrophy	0	0	3	4	7*	1	1	0	1	8*
Eosinophilic foci	0	1	0	6	8*	1	0	0	–0	1
Bile duct proliferation	6	4	5	3	7	5	4	4	8	11*
Mixed-cell foci	0	0	2	4*	5*	0	0	0	0	2
Biliary cyst	0	1	2	1	4*	3	8	5	7	7
Pericholangitis	1	1	2	1	4	0	1	0	4	0
Kidney										
Tubular cast	0	0	0	1	0	2	1	2	6	10*
Tubular atrophy	2	1	2	1	0	4	1	5	8	12*

NS: not statistically significant; ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$

Source: Mellert & Hildebrand (1994f)

The incidence and severity of hepatocellular hypertrophy were dose dependent and increased in animals of both sexes (males: 0/20 at 0 ppm, 0/20 at 200 ppm, 3/20 at 800 ppm, 4/20 at 8000 ppm and 7/20 at 16 000 ppm; females: 1/20 at 0 ppm, 1/20 at 200 ppm, 0/20 at 800 ppm, 1/20 at 8000 ppm and 8/20 at 16 000 ppm); however, statistical significance was achieved only at 16 000 ppm in animals of both sexes. Statistically significant increases in the incidence and severity of eosinophilic foci (0/20 at 0 ppm, 6/20 at 8000 ppm and 8/20 at 16 000 ppm) and mixed-cell foci (0/20 at 0 ppm, 4/20 at 8000 ppm and 5/20 at 16 000 ppm) were observed in males at 16 000 ppm. Evidence of a proliferative response in bile duct cells was associated with increased incidences of biliary cysts in males at 16 000

ppm (0/20 in controls versus 4/20 at 16 000 ppm) and in females at 8000 and 16 000 ppm (3/20 in controls versus 7/20 at both 8000 and 16 000 ppm). Bile duct proliferation in females (5/20 in controls versus 8/20 and 11/20 at 8000 and 16 000 ppm, respectively) was observed with statistical significance at 16 000 ppm. Statistically significantly increased incidences of tubular casts of the kidneys (2/20 in controls versus 10/20 at 16 000 ppm) and tubular atrophy of the kidney (4/20 in controls versus 12/20 at 16 000 ppm) were seen in females at 16 000 ppm. Increased incidences of lesions in other tissues were age related or independent of dose and were not considered to be toxicologically relevant (Table 18).

Histopathological re-evaluation of liver tissue slides from this study was conducted by a reviewing pathologist (Harada, 1995). The results are shown in Table 19.

Table 19. Incidence of hepatocellular tumours and number of rats with hepatocellular tumours in a 24-month toxicity study: re-evaluation of liver tissues

Tumour	Incidence of liver tumours									
	Males					Females				
	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm
No. of livers examined	20	20	20	20	20	20	20	20	20	20
Hepatocellular adenoma	0	0	0	2	2	0	0	1	4	4
Hepatocellular carcinoma	0	1	1	2	2	0	0	1	1	2
Total no. of animals with hepatocellular tumours	0	1	1	4	4	0	0	2	5*	6*#

ppm: parts per million; *: $P < 0.05$ (chi-squared test); #: $P < 0.05$ (Fisher exact probability test)

Source: Harada (1995)

A pathology working group (PWG) (Hildebrandt et al., 1995a) reviewed the original report (Mellert & Hildebrand, 1994f) as well as the reviewer's report (Harada, 1995). The objective of the PWG was to provide a consensus diagnosis for hepatocellular neoplasms. The PWG diagnosed the presence of both hepatocellular adenoma and hepatocellular carcinoma in the same animal. Multiple tumours of the same type were not recorded. The incidence of hepatocellular neoplasms is given in Table 20.

Other lesions, such as foci of cellular alteration of various types, hepatocellular hypertrophy (primarily periportal), cystic degeneration, angiectasis and/or biliary proliferative lesions, were commented on, particularly when such lesions had an impact on the interpretation of neoplasms. The PWG did not review all the liver slides or all examples of non-neoplastic liver lesions.

The results of the PWG review of proliferative hepatocellular lesions confirmed the increased incidence of hepatocellular neoplasms in male and female rats at 8000 and 16 000 ppm, as reported by the study and by the reviewing pathologist. The differences between the reviews lay primarily in the diagnosis of hepatocellular adenomas and carcinomas.

The NOAEL for toxicity was 800 ppm (equal to 36 mg/kg bw per day), on the basis of increased activity of serum GGT, increased relative liver weight, and increased incidence and degree of severity of eosinophilic and mixed-cell foci in males at 8000 ppm (equal to 370 mg/kg bw per day). The NOAEL for carcinogenicity was also 800 ppm (equal to 36 mg/kg bw per day), on the basis of an increased

incidence of hepatocellular tumours in animals of both sexes at 8000 ppm (equal to 370 mg/kg bw per day) (Mellert & Hildebrand, 1994f).

Table 20. Incidence of liver tumours in the 24-month toxicity study in rats

	Incidence of liver tumours									
	Males					Females				
	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm
No. of animals	20	20	20	20	20	20	20	20	20	20
Hepatocellular adenoma	0	0	0	1	4	0	0	1	4	4
(one-sided P-value)	–	(1)	(1)	(0.5)	(0.053)	–	(1)	(0.5)	(0.053)	(0.053)
Hepatocellular carcinoma	0	1	1	3	3	0	0	1	2	3
(one-sided P-value)	–	(0.5)	(0.5)	(0.115)	(0.115)	–	(1)	(0.5)	(0.244)	(0.115)
Hepatocellular tumours	0	1	1	4	7**	0	0	2	5*	6**
(one-sided P-value)	–	(0.5)	(0.5)	(0.053)	(0.004)	–	(1)	(0.244)	(0.024)	(0.01)

ppm: parts per million; *: $P \leq 0.5$; **: $P \leq 0.01$ (Fisher's exact test, one-sided)

Source: Hildebrandt et al. (1995a)

In a 24-month study of carcinogenicity, groups of 50 male and 50 female Wistar (Chbb:THOM(SPF)) rats (aged 42 days; mean body weights 192 g for males and 149 g for females) were fed diets containing kresoxim-methyl (purity 92.7–96.6%) at a concentration of 0, 200, 800, 8000 or 16 000 ppm (equal to 0, 9, 36, 375 and 770 mg/kg bw per day for males and 0, 12, 47, 497 and 1046 mg/kg bw per day for females, respectively). The animals were observed for clinical signs, death, feed consumption, body weight, and haematological and histopathological end-points. Blood samples for haematology were collected at the end of the study.

There were no treatment-related effects on mortality rates or clinical signs. The survival rates of males until day 735 were 70%, 72%, 74%, 74% and 70% at 0, 200, 800, 8000 and 16 000 ppm, respectively. In females, the survival rates until day 375 were 66%, 70%, 78%, 74% and 78% at 0, 200, 800, 8000 and 16 000 ppm, respectively. The terminal body weights and body weight gains were statistically significantly reduced in animals of both sexes at 8000 ppm (9% and 13% in males and 13% and 20% in females, respectively) and 16 000 ppm (9% and 12% in males and 14% and 21% in females, respectively). No statistically significant change in feed consumption was observed. Statistically significantly increased relative liver weights were observed in males at 16 000 ppm. Microscopic examination revealed hepatic neoplasia; increased incidences of hepatocellular carcinoma were observed in animals of both sexes at 8000 and 16 000 ppm (males: 7/50 at 0 ppm, 5/50 at 200 ppm, 2/50 at 800 ppm, 18/50 at 8000 ppm and 11/50 at 16 000 ppm; females: 1/50 at 0 ppm, 1/50 at 200 ppm, 2/50 at 800 ppm, 13/50 at 8000 ppm and 16/50 at 16 000 ppm). The number of animals with adenoma plus carcinoma in the liver was statistically significantly increased among males at 8000 ppm (8/50 at 0 ppm, 19/50 at 8000 ppm and 13/50 at 16 000 ppm) and among females at 8000 and 16 000 ppm (1/50 in controls versus 15/50 and 17/50 at 8000 and 16 000 ppm, respectively). The incidence of hepatocellular hypertrophy was increased in males at 8000 and 16 000 ppm and in females at 16 000 ppm, but reached statistical significance only in males at 16 000 ppm (males: 3/50 at 0 ppm, 5/50 at 8000 ppm and 10/50 at 16 000 ppm; females: 5/50 at 0 ppm and 7/50 at 16 000 ppm). There were dose-

dependent increases in the incidences of eosinophilic foci (males: 1/50 at 0 ppm, 5/50 at 8000 ppm and 11/50 at 16 000 ppm; females: 3/50 at 0 ppm, 8/50 at 8000 ppm and 5/50 at 16 000 ppm) and mixed-cell foci in animals of both sexes (males: 4/50 at 0 ppm, 9/50 at 8000 ppm and 12/50 at 16 000 ppm; females: 0/50 at 0 ppm and 5/50 at 16 000 ppm); however, statistically significant results were observed only at 16 000 ppm. There was evidence of alterations in bile duct cells, including an increased incidence of bile duct proliferation in females at 16 000 ppm (10/50 in controls versus 28/50 at 16 000 ppm), cholangiofibrosis in females at 16 000 ppm (1/50 in controls versus 7/50 at 16 000 ppm) and biliary cysts in males at 8000 ppm (males: 1/50 at 0 ppm, 7/50 at 8000 ppm and 6/50 at 16 000 ppm; females: 8/50 at 0 ppm, 12/50 at 8000 ppm and 15/50 at 16 000 ppm). Other non-neoplastic lesions included tubular mineralization of the kidneys in males at 16 000 ppm (6/50 in controls versus 18/50 at 16 000 ppm). The tubular mineralization was dose related and considered to be related to treatment. The lesions observed in other tissues were considered to be independent of dose and age related. The details are given in Table 21.

Table 21. Incidence of neoplastic and non-neoplastic findings in the liver and kidney in rats in a 24-month carcinogenicity study (original report)

Finding	Incidence of finding									
	Males					Females				
	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm
<i>No. of animals examined</i>	50	50	50	50	50	50	50	50	50	50
Liver										
Adenoma	1	0	0	1	0	0	1	2	2	1
Carcinoma	7	5	2	18*	13	1	1	2	13**	16**
Adenoma + carcinoma	8	5	2	19*	13	1	2	4	15**	17**
Cellular hypertrophy	3	2	2	5	10**	5	3	4	2	7
Eosinophilic foci	1	0	3	5	11**	3	0	3	8	5*
Mixed-cell foci	4	1	2	9	12**	0	0	0	3	5
Bile duct proliferation	14	21	17	12	17	10	13	12	13	28**
Cholangiofibrosis	13	12	16	8	17	1	4	1	5	7
Biliary cyst	1	4	5	7	6	8	10	10	12	15
Kidney										
Tubular mineralization	6	3	6	10	18	48	50	50	50	50

ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$

Source: Mellert & Hildebrand (1994g)

Histopathological re-evaluation of liver tissue slides from this study was conducted by a reviewing pathologist (Harada, 1995). The results are shown in Table 22.

Table 22. Incidence of hepatocellular tumours in rats in a 24-month carcinogenicity study

Tumour type	Incidence of liver tumours									
	Males					Females				
	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm
No. of livers examined	50	50	50	50	50	50	50	50	50	50
Hepatocellular adenoma	2	3	1	6	7	0	1	4	11**(***)	9**(***)
Hepatocellular carcinoma	4	3	1	9	7	1	0	1	6	7(*)
Total no. of animals with hepatocellular tumours	6	6	2	15**(***)	12	1	1	5	16**(***)	16(***)

*, $P < 0.05$; **, $P < 0.01$ (chi-squared test); (*): $P < 0.05$; (**): $P < 0.01$ (Fisher exact probability test)

Source: Harada (1995)

A PWG (Hildebrandt et al., 1995b) reviewed the original report (Mellert & Hildebrandt, 1994g) as well as the reviewer's report (Harada, 1995). The objective of the PWG was to provide a consensus diagnosis for hepatocellular neoplasms. The PWG diagnosed the presence of both hepatocellular adenoma and hepatocellular carcinoma in the same animal. Multiple tumours of the same type were not recorded. The incidence of hepatocellular neoplasms is given in Table 23.

Table 23. Incidence of liver tumours in the 24-month carcinogenicity study in rats (re-evaluation)

Tumour type	Incidence of liver tumours									
	Males					Females				
	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm
No. of animals	50	50	50	50	50	50	50	50	50	50
Adenoma, hepatocellular	2	2	0	5	4	0	2	4	11**	11**
(one-sided P -value)	–	(0.691)	(1)	(0.218)	(0.339)	–	(0.248)	(0.059)	(0.000)	(0.000)
Carcinoma, hepatocholangiocellular	0	0	0	0	1	–	–	–	–	–
(one-sided P -value)	–	(1)	(1)	(1)	(0.5)	–	–	–	–	–
Carcinoma, hepatocellular	4	4	2	12*	8	1	0	1	7	7
(one-sided P -value)	–	(0.643)	(0.898)	(0.027)	(0.178)		(1)	(0.753)	(0.030)	(0.030)
Carcinoma, hepatocellular and/or cholangiocellular	4	4	2	12*	9	–	–	–	–	–
(one-sided P -value)	–	(0.643)	(0.898)	(0.027)	(0.117)	–	–	–	–	–
Hepatocellular tumours	6	6	2	16*	11	1	2	5	16**	17**
(one-sided P -value)	–	(0.62)	(0.97)	(0.014)	(0.143)	–	(0.5)	(0.102)	(0.000)	(0.000)

*, $P < 0.05$; **, $P < 0.01$ (Fisher's exact test, one-sided)

Source: Hildebrandt et al. (1995b)

The NOAEL for toxicity was 800 ppm (equal to 36 mg/kg bw per day), on the basis of reduced body weight and body weight gain and hepatic alterations at 8000 ppm (equal to 375 mg/kg bw per day). The NOAEL for carcinogenicity was also 800 ppm (equal to 36 mg/kg bw per day), on the basis of increased incidences of hepatocellular tumours at 8000 ppm (Mellert & Hildebrand, 1994g, 1995b,c).

A histopathological re-evaluation of the hepatocellular tumour incidence in the two studies (Mellert & Hildebrand, 1994f,g) in rats was conducted by a PWG (Hildebrandt et al., 1995c). The combined incidence of liver tumours is shown in Table 24. Concurrent reassessment revealed similar dose-response relationships in the occurrence of hepatocellular carcinoma, and the statistically significant results with the combined data clearly indicate the hepatic carcinogenic potential of kresoxim-methyl in rats (Van Ravenzwaay, 1996).

Table 24. Combined incidence of liver tumours in the 24-month carcinogenicity and chronic toxicity studies in rats

Tumour type	Incidence of liver tumours									
	Males					Females				
	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm	0 ppm	200 ppm	800 ppm	8 000 ppm	16 000 ppm
Total no. of animals	70	70	70	70	70	70	70	70	70	70
Hepatocellular adenoma	2 (2.9%)	2 (2.9%)	0 (0%)	6 (8.6%)	8 (11.4%)	0 (0%)	2 (2.9%)	5* (7.1%)	15** (21%)	15** (21%)
(one-sided P-value)	(PWG conclusion)	(0.690)	(1)	(0.137)	(0.048)		(0.248)	(0.029)	(0.000)	(0.000)
Hepatocellular carcinoma	4 (5.7%)	5 (7.1%)	3 (4.3%)	15** (21.4%)	12 (17.1%)	1 (1.4%)	0 (0%)	2 (2.9%)	9** (12.8%)	10** (14.2%)
(one-sided P-value)		(0.5)	(0.78)	(0.006)	(0.03)		(1)	(0.5)	(0.009)	(0.004)
Hepatocellular tumours	6	7	3	20**	18**	1	2	7*	21**	23**
(one-sided P-value)		(0.5)	(0.917)	(0.002)	(0.006)		(0.5)	(0.031)	(0.000)	(0.000)

ppm: parts per million; *: $P < 0.05$; **: $P < 0.01$ (Fisher's exact test, one-sided)

Source: Hildebrandt et al. (1995c)

The conclusion drawn in the Hildebrandt et al. (1995c) report is essentially the same as that drawn in the original reports – that is, kresoxim-methyl has a carcinogenic effect on the liver of male and female rats at doses of 8000 and 16 000 ppm. There was a slight numeric, but not statistically significant (level of significance did not reach $P < 0.01$), increase in the incidence of hepatocellular adenomas alone or in combination with hepatocellular carcinomas in females treated with 800 ppm, which was seen only when the incidences of the chronic toxicity and carcinogenicity studies were combined. There was no increase in the incidence of hepatocellular carcinomas alone. The PWG considered this to be an equivocal response.

The actual incidence at 800 ppm in the combined evaluation of the long-term rat studies was 5/70 females (for adenomas), or approximately 7% (Table 24). Weak statistical significance ($P < 0.05$, but not reaching the $P < 0.01$ level, which was considered by the PWG to be required for this common neoplasia) was achieved only because the control incidence was unusually low (0%). Contemporary

historical control data for liver adenomas in female Wistar rats in BASF's laboratories (Table 25) include a total of 38 long-term toxicity studies. In these studies, the number of liver adenomas in female control animals was 43/1620 animals, which is equivalent to 2.7%. This indicates that normally in a group of 70 female control animals, approximately two would have been found to have a liver adenoma. Clearly, there is no statistically, or biologically, significant difference between 2/70 (the historical mean) and 5/70 animals (the actual number at 800 ppm). Moreover, the historical data of BASF's laboratories also demonstrate that the maximum incidence of liver adenoma in control female Wistar rats can be as high as 20%, indicating that the 7% noted in the kresoxim-methyl studies at 800 ppm is well within the historical range. Similarly, the incidence of combined liver adenomas and carcinomas in the controls (1.4%) was also lower than the historical mean of 3.4%. Again, the actual study incidence at 800 ppm (10%) is well within the historical range (up to 22%). Therefore, it is concluded that a carcinogenic potential in the liver of Wistar rats exists only at doses of 8000 ppm and higher.

Table 25. Historical control data from the BASF test facility (1997)^a

Tumour type	Incidence of liver tumours					
	Males			Females		
	Mean	Minimum	Maximum	Mean	Minimum	Maximum
Hepatocellular adenoma	120/1 620 (7.4%)	0/100 (0%)	15/50 (30%)	43/1 620 (2.7%)	0/100 (0%)	10/50 (20%)
Hepatocellular carcinoma	62/1 620 (3.8%)	0/50 (0%)	6/50 (12%)	12/1 620 (0.7%)	0/100 (0%)	3/60 (5%)
Hepatocellular tumours	182/1 620 (11.2%)	0/50 (0%)	16/50 (32%)	55/1 620 (3.4%)	0/100 (0%)	11/50 (22%)

^a *n* = 38 studies; 1620 rats of each sex evaluated.

Source: Hildebrandt et al. (1995c)

To investigate the tumours seen in earlier carcinogenicity (Mellert & Hildebrand, 1994g) and chronic toxicity studies (Mellert & Hildebrand, 1994f), which were performed in Wistar rat strain Chbb:THOM (Dr. Karl Thomae GmbH, Biberach/Riss), another study was conducted using Wistar rat strain CrIGlxBrIHan:WI (Charles River Germany). The objective of this additional study was to determine whether the test substance exhibits a carcinogenic potential when administered in the diet to Wistar rats of the strain CrIGlxBrIHan:WI for the major part of their lifespan.

In this additional study, kresoxim-methyl (lot/batch no. COD-000225; purity 97.8%) was administered to Wistar rats (CrIGlxBrIHan:WI; aged 42 ± 1 days; body weight 154.6 ± 7.2 g and 156.0 ± 7.9 g for males at 0 and 16 000 ppm, respectively, and 127.6 ± 6.5 g and 126.3 ± 6.1 g for females at 0 and 16 000 ppm, respectively) in the feed at a concentration of 0 or 16 000 ppm (equal to 752.1 mg/kg bw per day for males and 1021.6 mg/kg bw per day for females) over a period of 24 months. Each group consisted of 50 animals of each sex. Feed consumption and body weight were determined once a week during the first 13 weeks and at 4-week intervals thereafter. The animals were examined for signs of toxicity or mortality at least once a day; moreover, detailed clinical examinations in an open field were conducted prior to the start of the administration period and weekly thereafter. Differential blood counts were determined for all surviving animals at the end of the study and also from all animals killed in extremis during the study. After about 24 months, the animals were subjected to gross pathological assessment, followed by histopathological examination.

Treatment did not affect clinical signs of toxicity, except for statistically significantly decreased feed consumption, body weight and body weight change. The survival of the animals was not adversely affected by the test substance administration. Clinical pathology showed no treatment-related effects regarding haematology. At the only dose tested, an increase in liver tumours (hepatocellular adenoma and carcinoma) was observed. This increase was statistically significant for hepatocellular carcinomas

in male animals and clearly above historical control values. For female animals, the tumour incidences were not statistically significantly increased and only slightly outside the historical control range in the case of hepatocellular adenoma (Tables 26 and 27).

Table 26. Neoplastic and non-neoplastic changes in the liver of rats administered kresoxim-methyl in the diet for 24 months

Finding	Incidence of finding			
	Males		Females	
	0 ppm	16 000 ppm	0 ppm	16 000 ppm
Number of animals	50	50	50	50
Non-neoplastic findings				
Hypertrophy peripheral	–	6*	–	12**
Eosinophilic foci	26	41**	7	30**
Basophilic foci	2	6	–	14**
Neoplastic findings				
Hepatocellular adenoma	0	3	0	4
Hepatocellular carcinoma	3	13**	1	3
Total tumours (adenoma + carcinoma)	3	16**	1	7*

ppm: parts per million; *: $P \leq 0.05$; **: $P \leq 0.01$ (Fisher's exact test, one-sided)

Source: Kamp et al. (2008)

Table 27. Historical control data: hepatocellular tumours^a

Tumour type	Incidence of liver tumours					
	Males			Females		
	Mean	Minimum	Maximum	Mean	Minimum	Maximum
Hepatocellular adenoma	7/350 (2.0%)	0/50 (0.0%)	2/50 (4.0%)	3/350 (0.9%)	0/50 (0.0%)	3/50 (6.0%)
Hepatocellular carcinoma	3/350 (0.9%)	0/50 (0.0%)	2/50 (4.0%)	5/350 (1.4%)	0/50 (0.0%)	3/50 (6.0%)
Combined tumours	10/350 (2.9%)	0/50 (0.0%)	3/50 (6.0%)	8/350 (2.3%)	0/50 (0.0%)	3/50 (6.0%)

^a Seven 24-month studies (oral diet) started at the test facility between 1999 and 2005; 50 Wistar rats (Charles River Germany) of each sex per study.

Source: BASF (2018b)

Additionally, non-neoplastic findings in the liver (eosinophilic foci and basophilic foci) were increased in both sexes compared with the control group (Table 26).

Overall, the liver carcinogenicity of kresoxim-methyl was confirmed for male rats; the slight increase in female hepatocellular tumours was not statistically significant. The strain CrLGlxBr/Han:WI was not less sensitive than the Wistar rat strain Chbb:THOM with respect to the carcinogenic potential of kresoxim-methyl in the liver of both male and female rats (Kamp et al., 2008).

2.4 Genotoxicity

Kresoxim-methyl was tested for genotoxicity in an adequate range of in vitro and in vivo assays. It gave a positive response only in one in vitro assay (the Syrian hamster embryo cell transformation assay) and was negative in all other in vitro assays and all in vivo assays. The details are provided in Table 28.

Table 28. Overview of genotoxicity tests with kresoxim-methyl

End-point	Test object	Concentration	Purity (%)	Results	Reference
In vitro					
Bacterial reverse mutation assay (Ames test)	<i>Salmonella typhimurium</i> strains TA98, TA100, TA1535, TA1537; <i>Escherichia coli</i> strain WP2uvrA; plate incorporation and preincubation assay; with/without S9 mix	20, 100, 500, 2 500, 5 000 µg/plate	93.7	Negative	Engelhardt & Hoffmann (1993a)
Bacterial reverse mutation assay (Ames test)	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537; <i>E. coli</i> strain WP2uvrA; plate incorporation and preincubation assay; with/without S9 mix	0, 20, 100, 500, 2 500, 5 000 µg/plate	94.3	Negative	Engelhardt & Hildebrand (1994)
Bacterial reverse mutation assay (Ames test)	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, standard plate test; <i>E. coli</i> WP2uvrA, preincubation test	33–6 000 µg/plate	86.4	Negative	Woitkowiak (2011)
Chromosomal aberration assay in mammalian cells	Human lymphocytes; with/without S9 mix	0, 2.5, 5, 10, 20, 40 µg/mL	98.7	Negative	Hoffmann & Engelhardt (1993)
Morphological transformation assay in mammalian cells	Syrian hamster embryo cells	0, 0.01, 0.025, 0.05, 0.1, 0.2, 0.3, 0.4 µg/mL (7-day experiment) 0, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 5.0 µg/mL (24-hour experiment)	97.8	Positive ^a	Schwindt & Landsiedel (2008)
Forward mutation assay in mammalian cells (HPRT test)	CHO-K1 cells; with/without S9 mix	0, 0.1, 0.5, 1, 2.15, 4.64, 5, 10, 21.5, 46.4, 50, 100 µg/mL	94.3	Negative	Polloth & Hoffmann (1994a)
Unscheduled DNA synthesis	Rat hepatocytes; with/without S9 mix	0, 0.33, 1, 3.3, 10, 33, 100 µg/mL	94.3	Negative	Polloth & Hoffmann (1994b)

End-point	Test object	Concentration	Purity (%)	Results	Reference
in mammalian cells					
In vivo					
Micronucleus test	NMRI mouse, male and female (single intraperitoneal administration; vehicle 0.5% aqueous carboxymethylcellulose)	0, 500, 1 000, 2 000 mg/kg bw	94.3	Negative	Engelhardt & Hoffmann (1993b)
Micronucleus test	CrI:NMRI male mice (single oral administration; vehicle corn oil)	0, 500, 1 000, 2 000 mg/kg bw	86.4	Negative	Schulz & Landsiedel (2011)
Micronucleus test	Wistar rat, male and female (single intraperitoneal administration; vehicle 0.5% aqueous carboxymethylcellulose)	0, 500, 1 000, 2 000 mg/kg bw	94.9	Negative	Hoffmann & Engelhardt (1997)
Ex vivo unscheduled DNA synthesis (and S-phase response)	Wistar rat, male (single oral gavage); analysis of rat hepatocytes prepared 18 hours after exposure	0, 20, 200, 1 000 mg/kg bw	94.3	Negative	Polloth & Hoffmann (1994c)
Ex vivo unscheduled DNA synthesis	Wistar rat, male (3-week dietary administration); analysis of rat hepatocytes prepared 16 hours after last exposure	0, 200, 16 000 ppm (0, 10, 800 mg/kg bw per day)	94.3	Negative	Polloth & Hoffmann (1994d)
Chromosomal aberration assay in germ cells	NMRI mouse, male (single oral gavage); analysis of spermatogonial cells	0, 500, 1 000, 2 000 mg/kg bw	95.0	Negative	Honarvar (2002)

bw: body weight; CHO: Chinese hamster ovary; DNA: deoxyribonucleic acid; HPRT: hypoxanthine–guanine phosphoribosyltransferase; MTF: morphological transformation frequency; RPE: relative plating efficacy; S9: 9000 × g supernatant fraction from rat liver homogenate

^a Induces morphological transformations. No relevant increase in the number of transformed colonies was observed after an exposure period of 7 days. After an exposure time of 24 hours, a clear increase in the number of transformed colonies was observed beginning at the lowest tested concentration of 0.25 µg/mL, with an MTF of 1.12%, up to the highest response of 2.14% MTF at a concentration of 1.5 µg/mL. The RPE was reduced from about 0.2 µg/mL onward (RPE 79.8%) after the 7-day exposure and from about 2.0 µg/mL onward (RPE 66.9%) after the 24-hour exposure. Colony size and density were reduced from about 0.2 µg/mL onward after the 7-day exposure and from about 2.0 µg/mL onward after the 24-hour exposure. According to the results of the present in vitro study, the test substance kresoxim-methyl led to a clear, statistically significant increase in the number of morphologically transformed colonies, but in the 24-hour exposure only. All tested concentration groups (except 5.0 µg/mL, where the cytotoxicity was too strong to allow colony formation) showed a transformation frequency above 0.6%, which is the criterion for a positive response and is above the historical negative control range as well. A desired negative response in at least one of the lower concentrations could not be achieved, even though a wide concentration range was applied. In the experiment with the 7-day exposure, no relevant increase was observed. The increase in the transformation frequency induced by the positive control agent benzo(a)pyrene clearly demonstrated the sensitivity of the test method and of the metabolic activity of the Syrian hamster embryo cells. Thus, under the experimental conditions chosen here, kresoxim-methyl induces morphological transformation in Syrian hamster embryo cells in vitro.

When kresoxim-methyl was assessed for its potential to induce morphological transformation in Syrian hamster embryo cells, it was considered to cause a significant increase in transformed colonies. The Syrian hamster embryo transformation assay investigates morphological transformation,

not DNA or chromosomal damage, it is an old study design and there is currently no Organisation for Economic Co-operation and Development (OECD) test guideline for it.

2.5 Reproductive and developmental toxicity

(a) Multigeneration studies

Rats

In a two-generation study of reproductive toxicity, groups of 25 male and 25 female Wistar (Chbb:THOM(SPF)) rats (35–36 days old; mean body weights 142.9 g for males and 125.4 g for females) were fed diets containing kresoxim-methyl (purity >93.7%) at a concentration of 0, 50, 1000, 4000 or 16 000 ppm. The F₀ generation was exposed directly, the F_{1a} and F_{1b} generations directly and indirectly (through lactation) and the F₂ generation indirectly. The mean daily intakes of kresoxim-methyl are shown in Table 29.

Table 29. Mean daily intakes of kresoxim-methyl in a reproductive toxicity study in rats

Generation/sex/period	Mean intake (mg/kg bw per day)			
	50 ppm	1 000 ppm	4 000 ppm	16 000 ppm
F ₀ males	5.1	102.6	411.0	1 623.1
F ₀ female (premating)	5.6	106.7	437.2	1 741.1
F ₀ female F _{1a} litter	Gestation period	4.6	91.7	483.8
	Lactation period	8.3	162.0	661.8
F ₀ female F _{1b} litter	Gestation period	4.3	84.3	348.9
	Lactation period	7.1	143.2	587.2

bw: body weight; F₀: parental generation; F₁: first filial generation; ppm: parts per million

Source: Hellwig & Gelbke (1994a)

The parental rats were observed for clinical signs, death, feed consumption, body weight, and clinical chemistry, histopathological and reproductive parameters, including mating, fertility, gestation and live birth indices. The litters and pups were observed for viability, lactation, behaviour and developmental indices, including pinna unfolding and opening of the auditory canal and eyes. The functional tests included grip strength, startle reflex and pupillary reflex. Reproductive organs and the pituitary, liver and kidney were examined histopathologically. The clinical chemistry end-points included assays for serum ALT, AST, ALP and GGT activities.

No compound-related clinical signs or deaths were observed in the F₀, F₁ or F₂ generation throughout the study. F₀ and F₁ parental animals showed no effects on mating, fertility, gestation or live birth indices, but statistically significant reductions in feed consumption were observed in F₀ and F₁ males during treatment and in F₀ and F₁ females during gestation and lactation at 16 000 ppm. Statistically significant reductions in body weight were seen at doses of 4000 ppm and higher in F₀ and F₁ males and in F₀ and F₁ females during gestation and lactation of the F_{1a} and F_{1b} generations. Statistically significant reductions in body weight gain were also observed in F₀ and F₁ males at these doses and in F₀ females at 16 000 ppm during the premating period before the first gestation. Statistically significant reductions in the activities of ALT and ALP were observed in F₀ and F₁ parents of both sexes, although these reductions may not be toxicologically relevant (Moss, 1994; Mellert & Hildebrand, 1995d). The activity of GGT was statistically significantly increased in F₀ males at 4000 ppm and higher and in F₁ animals of both sexes at 16 000 ppm. Statistically significantly decreased numbers of fat storage cells were observed in the livers of F₀ and F₁ males at 4000 ppm and higher; however, this change may have occurred as a result of the reduced feed consumption at higher doses.

Statistically significant increases in relative kidney weights were observed in F₀ males at 16 000 ppm and in F₀ females and F₁ males at 4000 ppm and higher. No treatment-related morphological lesions were observed in the liver or kidney.

No compound-related changes in clinical signs, sex ratio, viability index or lactation index were seen in pups of the F_{1a}, F_{1b} or F_{2a} generations. Body weights and body weight gains during lactation were statistically significantly decreased in F_{1a}, F_{1b} and F_{2a} pups at 4000 ppm and higher. A statistically significantly lower percentage of F_{1b} pups at these doses had pinna unfolding; statistically significant retardations in opening of the auditory canal and eyes were also observed in F_{1b} and F_{2a} pups at 4000 ppm, but these were not dose dependent (Table 30). There were no differences in the results of reflex tests between controls and treated animals in any generation. Necropsy of pups revealed no external abnormalities.

Table 30. Physical development and reflex indices in pups from the F₀ females for the F_{1b} generation

Parameter			0 ppm	50 ppm	1 000 ppm	4 000 ppm	16 000 ppm
Pinna unfolding	Litters tested	<i>N</i>	25	24	25	23	24
	Pups tested	<i>N</i>	362	349	380	333	364
	Pups meeting criteria	<i>N</i>	329	325	347	251	289
		%	91	93	91	75	79
	Pups meeting criteria/litter	Mean %	92.9	92.5	89.7	77.0**	79.5*
		SD	24.78	22.33	28.80	35.09	34.26
Auditory canal opening	Litters tested	<i>N</i>	25	24	25	23	24
	Pups tested	<i>N</i>	197	191	197	179	186
	Pups meeting criteria	<i>N</i>	195	189	186	175	175
		%	99	99	94	98	94
	Pups meeting criteria/litter	Mean %	99.0	99.0	94.5	97.8	93.8
		SD	3.46	5.10	20.44	4.84	18.85
Eye opening	Litters tested	<i>N</i>	25	24	25	23	24
	Pups tested	<i>N</i>	197	191	197	179	186
	Pups meeting criteria	<i>N</i>	193	174	172	154	170
		%	98	91	87	86	91
	Pups meeting criteria/litter	Mean %	98.0	91.1	87.5	86.4*	91.7
		SD	6.92	23.16	29.32	23.81	22.62

N: number; ppm: parts per million; SD: standard deviation; *: $P \leq 0.05$; **: $P \leq 0.01$ (Wilcoxon test, one-sided)

Source: Hellwig & Gelbke (1994a)

The NOAEL for parental toxicity was 1000 ppm (equal to 84.3 mg/kg bw per day), based on reduced body weight and body weight gain, increased serum GGT activity and increased relative kidney weights at 4000 ppm (equal to 348.9 mg/kg bw per day). The NOAEL for reproductive toxicity was 16 000 ppm (equal to 1389.3 mg/kg bw per day), the highest dose tested, as no reproductive effects were observed at any dose. The NOAEL for offspring toxicity was 1000 ppm (equal to 84.3 mg/kg bw

per day), based on retarded growth in pups leading to a lower rate of F_{1b} pups per litter with pinna unfolding at 4000 ppm (equal to 348.9 mg/kg bw per day) (Hellwig & Gelbke, 1994a).

(b) *Developmental toxicity*

Rats

Groups of 25 female Wistar (Chbb:THOM(SPF)) rats were given kresoxim-methyl (purity >93.7%) suspended in 0.5% carboxymethylcellulose by gavage at a dose of 0, 100, 400 or 1000 mg/kg bw per day on days 6–15 of gestation.

No treatment-related changes in clinical signs, mortality rates, body weight or feed consumption were observed in maternal animals. There were no differences in conception rate, mean numbers of corpora lutea, total implantations, resorptions, preimplantation or postimplantation losses, or live fetuses. No statistically significant differences in fetal sex ratio, placental weight or fetal weight were observed between control and treated groups.

External examination revealed three fetuses with external malformations: one fetus at 100 mg/kg bw per day had anasarca and a cleft palate, one fetus at 400 mg/kg bw per day was acaudate and one fetus at 1000 mg/kg bw per day had meningocele and unilateral microphthalmia; however, the incidence of these malformations was within the range for historical controls. One fetus at 1000 mg/kg bw per day had hydrocephalus, but this incidence was also within the historical control range. An increased incidence of incompletely ossified thoracic vertebral bodies was seen in 13% of all fetuses and 56% of litters (statistically significant) at 1000 mg/kg bw per day (Table 31); the mean historical control values were 8% (0–49%) of all fetuses and 23% (0–100%) of litters.

Table 31. Ossification status of thoracic vertebrae in a developmental toxicity study in rats

Parameter			0 mg/kg bw per day	100 mg/kg bw per day	400 mg/kg bw per day	1 000 mg/kg bw per day
Litters evaluated	<i>N</i>		24	23	22	25
Fetuses evaluated	<i>N</i>		168	167	156	172
Live fetuses	<i>N</i>		168	167	156	172
Thoracic vertebral body/bodies incompletely ossified	Fetal incidence	<i>N</i>	12	12	12	23
		%	7.1	7.2	7.7	13
	Litter incidence	<i>N</i>	5	9	7	14*
		%	21	39	32	56
	Affected fetuses/litter	Mean %	6.9	6.9	7.9	14.2*
		SD	17.55	10.19	13.34	16.08
Thoracic vertebral body/bodies only one ossification centre	Fetal incidence	<i>N</i>	0	0	1	0
		%	0	0	0.6	0
	Litter incidence	<i>N</i>	0	0	1	0
		%	0	0	4.5	0
	Affected fetuses/litter	Mean %	0	0	0.5	0
		SD	0	0	2.37	0
Thoracic vertebral	Fetal incidence	<i>N</i>	0	0	1	0
		%	0	0	0.6	0

			0 mg/kg bw per day	100 mg/kg bw per day	400 mg/kg bw per day	1 000 mg/kg bw per day
Parameter						
body/bodies not ossified	Litter incidence	N	0	0	1	0
		%	0	0	4.5	0
	Affected fetuses/litter	Mean %	0	0	0.6	0
		SD	0	0	3.05	0

bw: body weight; N: number; SD: standard deviation; *: $P \leq 0.05$

Source: Hellwig & Gelbke (1994b)

The NOAEL for maternal toxicity was 1000 mg/kg bw per day, the highest dose tested. The NOAEL for embryo and fetal toxicity was 400 mg/kg bw per day, on the basis of a slight increase in incidence of reduced ossification in fetuses above the mean historical control value at 1000 mg/kg bw per day (Hellwig & Gelbke, 1994b).

Rabbits

Groups of 15 female Himalayan rabbits were given kresoxim-methyl (purity 96.6%) suspended in 0.5% carboxymethylcellulose by gavage at a dose of 0, 100, 400 or 1000 mg/kg bw per day on days 7–19 of gestation.

No compound-related changes in clinical signs, death, body weight or feed consumption were observed in maternal animals, and there were no compound-related changes in conception rate, mean numbers of corpora lutea, total implantations, resorptions, preimplantation or postimplantation losses, or live fetuses. No significant differences in fetal sex ratio, placental weight or fetal weight were observed between control and treated groups.

External examination revealed one fetus with microcephaly and brachygnathia at 100 mg/kg bw per day, but the incidence was within the range of historical control data. Eight fetuses (0/15, 2/15, 2/15 and 3/15 at 0, 100, 400 and 1000 mg/kg bw per day, respectively) had soft tissue malformations: at 100 mg/kg bw per day, one had a septal defect, and one had agnesis of the gall bladder (2.5% incidence); at 400 mg/kg bw per day, two had a septal defect (1.9%); and at 1000 mg/kg bw per day, one had a septal defect, dilatation of the aortic arch and an aorta descendens, one had hydrocephaly and one had agnesis of the gall bladder (4.1%). The percentage of soft tissue malformations in historical controls was 2.2–3.1%. The incidences of ventricular septal defects in the treated groups were comparable to historical control values. Increased incidences of fused sternbrae were observed in 3/15 controls, 11/15 at 100 mg/kg bw per day, 7/15 at 400 mg/kg bw per day and 9/15 at 1000 mg/kg bw per day; the increase at 100 mg/kg bw per day was statistically significant, but was within the historical control range. Increased total numbers of fetal malformations were also observed in treated groups, but again at incidence rates comparable with those of historical controls (0%, 4.9%, 3.8% and 4.1% at 0, 100, 400 and 1000 mg/kg bw per day, respectively, versus 2.9–3.5% for historical controls).

The NOAEL for both maternal and embryo/fetal toxicity was 1000 mg/kg bw per day, the highest dose tested (Hellwig & Hildebrand, 1993).

2.6 Special studies

(a) Neurotoxicity

Acute neurotoxicity

Kresoxim-methyl (purity 93.7%) was administered to groups of 10 male and 10 female Wistar (Chbb:THOM(SPF)) rats (42 days old; mean body weight 190 g for males and 147 g for females) as a

single oral administration by gavage at a dose of 0, 500, 1000 or 2000 mg/kg bw. The vehicle was 0.5% carboxymethylcellulose solution, and the dosing volume was 10 mL/kg bw.

The animals were observed for up to 2 weeks after dosing. Body weight was determined weekly. The general state of health was checked at least daily, and the animals were additionally examined and palpated once a week. Functional observational batteries and motor activity measurements were carried out on all animals 6 days prior to dosing, at day 0 (within a few hours of dosing) and 7 and 14 days after dosing. Five animals of each sex per dose were fixed by in situ perfusion and subjected to neuropathological examination.

No substance-related signs of neurotoxicity or any other signs of general toxicity were observed.

The NOAEL for both systemic toxicity and neurotoxicity under the conditions of this study was 2000 mg/kg bw, the highest dose tested (Mellert, Kaufmann & Hildebrand, 1996a).

Subchronic neurotoxicity

Kresoxim-methyl (purity 94.3%) was administered to groups of 10 male and 10 female Wistar (Chbb:THOM(SPF)) rats (49 days old; mean body weight 227 g for males and 167 g for females) for 3 months at a dietary concentration of 0, 1000, 4000 or 16 000 ppm (equal to 0, 72, 292 and 1180 mg/kg bw per day for males and 0, 84, 341 and 1354 mg/kg bw per day for females, respectively). Feed consumption and body weight were determined at least once a week. A check of the general state of health of the animals was made at least daily. Furthermore, the animals were examined and palpated once a week. In addition to this, general clinical examination and functional observational batteries and motor activity measurements were carried out on all animals before the start of the administration period and during weeks 4, 8 and 13 of the administration period. Five animals of each sex per dose were fixed by in situ perfusion and subjected to neuropathological examination.

In the 16 000 ppm group, there was a reduction in feed consumption in both sexes, which was statistically significant on some days only. The values were 8% (males) and 13% (females) below the control values. There was also a reduction in body weight in both sexes, which was statistically significant on some days only. The values were up to 9% below the control values. There was a decrease in body weight gain in both sexes, which was statistically significant on some days only. The values were 17% (males) and 32% (females) below the control values.

There were no substance-related effects in other groups. No signs of neurotoxicity were detected at any of the doses.

The NOAEL for neurotoxicity was 16 000 ppm (equal to 1180 mg/kg bw per day), the highest dose tested. The NOAEL for systemic toxicity was 4000 ppm (equal to 292 mg/kg bw per day), based on a reduction of body weight gain at 16 000 ppm (equal to 1180 mg/kg bw per day) (Mellert, Kaufmann & Hildebrand, 1996b).

(b) Mechanistic studies on the carcinogenic mode of action

Tumour initiating potential

Groups of 10 Wistar (Chbb:THOM) rats of each sex were subjected to a partial hepatectomy and 14 hours later received kresoxim-methyl (purity 94.3% and 99.4%) in a single gavage dose of 2388 mg/kg bw suspended in 0.5% carboxymethylcellulose. For promotion, phenobarbital was incorporated in the diet at a concentration of 500 ppm (equivalent to 25 mg/kg bw) for 8 weeks. Liver slices were examined histologically on slides stained with haematoxylin and eosin (H&E) or stained immunochemically for the placental form of glutathione S-transferase (GST-P). The incidences of hepatocellular alteration (foci) and of GST-P-positive foci were used to estimate initiating potential. *N*-Nitrosomorpholine was used as the positive control.

Hepatocellular hypertrophy was found in almost all of the phenobarbital-treated animals, and GST-P-positive foci and foci of hepatocellular alteration were found in nearly all animals treated with the positive control. The number of animals with GST-P-positive foci in groups treated with kresoxim-methyl was comparable with that of vehicle controls. The numbers of foci per liver in promoted animals were 0–3 in those given kresoxim-methyl, 0–10 in vehicle controls and 3–100 in positive controls.

The results suggest that kresoxim-methyl does not have tumour initiating potential in rats in this test (Gamer & Hildebrand, 1995a,b).

Tumour promoting potential

In a medium-term study of promotion, male Fischer (F344/DuCrj) rats (aged 4 weeks; body weight 55–65 g) were initiated with a single intraperitoneal injection of *N*-nitrosodiethylamine at a dose of 200 mg/kg bw. The animals were then maintained on basal diet ad libitum for 14 days. Five groups of 16 male rats were fed diets containing 0, 200, 800, 8000 or 16 000 ppm kresoxim-methyl (purity 95.4%) for 6 weeks, with average intakes of 0, 10.78, 42.47, 430.6 and 886 mg/kg bw per day, respectively (not adjusted for purity). The remaining 16 male rats were fed a diet containing 500 ppm phenobarbital (28 mg/kg bw per day) as a positive control for 6 weeks. The animals were subjected to a two-thirds partial hepatectomy after the first week of feeding with kresoxim-methyl or phenobarbital and were observed for clinical signs, death, feed consumption and body weight. The liver was examined grossly and histopathologically.

There were no compound-related deaths or clinical signs of toxicity. Body weight and feed consumption in groups given kresoxim-methyl were comparable with those of controls. Significant increases in the absolute and relative weights of the liver were observed in groups given kresoxim-methyl at 800 ppm and higher. Treatment with phenobarbital caused significant increases in body weight, feed consumption and relative liver weight. Quantification of hepatic foci with a computer-assisted image analyser revealed significant, dose-related increases in the number and area of GST-P-positive hepatocellular foci in groups given kresoxim-methyl at and above 8000 ppm, as well as in the phenobarbital-treated positive controls.

The NOAEL for foci promotion in F344 rats was 800 ppm (equal to 42.47 mg/kg bw per day) (Harada, Kawakatsu & Nagayoshi, 1997).

Hepatic cell proliferation

A series of studies was conducted to investigate the effect of kresoxim-methyl on hepatic cell proliferation in rats, by measuring S-phase DNA synthesis, an indicator of cell proliferation. Incorporation of 5-bromo-2'-deoxyuridine (BrdU) into DNA was measured by immunohistochemical staining.

In the first study, groups of five young (64 days old) male Wistar (Chbb:Thom(SPF)) rats were given diets containing kresoxim-methyl (purity 94.3%) at a concentration of 0, 200 or 16 000 ppm (equal to 0, 15 and 1100 mg/kg bw per day, respectively) for 3 weeks. Osmotic minipumps filled with BrdU were implanted subcutaneously 1 week before necropsy. The animals were observed for clinical signs, death, feed consumption and body weight. The livers were examined grossly and immunohistopathologically. Samples of the hepatic lobule and the jejunum were taken as positive tissues for proliferation and were stained with H&E and immunochemically with an antibody against BrdU. Immunopositive and H&E-counterstained hepatocyte nuclei from 11 fields for each of three lobes were counted.

No treatment-related changes in body weight, feed consumption or clinical signs were seen. A slight increase in liver weights was observed at 16 000 ppm, but no treatment-related gross lesions or histopathological changes were observed in the livers of treated rats. A statistically significant increase in the number of hepatocytes in which BrdU was incorporated into the DNA of S-phase cells was

observed in the periportal zone (zone 1) and the intermediate zone (zone 2) of the hepatic lobule in the group at 16 000 ppm. No significant increase in cell proliferation was observed in the group at 200 ppm (Polloth & Hildebrand, 1994a).

In a supplementary study with a similar design, groups of five young (56 days of age) male Wistar (Chbb:THOM) rats received kresoxim-methyl (purity 94.9%) in the diet at a concentration of 0, 800 or 8000 ppm (equal to 0, 61 and 603 mg/kg bw per day, respectively) for 3 weeks.

Results similar to those observed at 16 000 ppm in the first study were observed at 8000 ppm. Statistically significant increases in cell proliferation were observed in zones 1 and 2 of the hepatic lobule at 8000 ppm, but not at 800 ppm

Based on these findings, the NOAEL for hepatic cell proliferation was 800 ppm (equal to 61 mg/kg bw per day) (Mellert, Bahnemann & Hildebrand, 1997).

In a study of the hepatic proliferating activity of kresoxim-methyl (purity 94.3%) in the livers of older rats, groups of five male Wistar (Chbb) rats (aged 16 months) were given diets containing kresoxim-methyl (purity 94.3%) at a concentration of 0, 200 or 16 000 ppm (equal to 0, 15 and 1140 mg/kg bw per day, respectively) for 3 weeks. The design of the study was similar to those described above.

No compound-related changes in clinical signs or body weight were seen, and no compound-related lesions in the liver were observed by microscopic examination with H&E staining. A statistically significant increase in cell proliferation was observed in zone 1 of the hepatic lobule at 16 000 ppm, which was comparable with that observed in the young rats (Polloth & Hildebrand, 1994b).

In a study of the hepatic proliferating activity of kresoxim-methyl in the livers of rats treated for various periods, groups of five male Wistar (Chbb) rats (42 days old) were given diets containing kresoxim-methyl (purity 92.7%) at a concentration of 0 or 16 000 ppm (equal to 1660 mg/kg bw per day for 1 week; 1362 mg/kg bw per day for 6 weeks; and 1150 mg/kg bw per day for 13 weeks) for 1, 6 or 13 weeks. Groups were allowed to recover for 2 or 3 weeks.

Significant increases in cell proliferation were observed in the treated groups after 1 week (zones 1, 2 and 3) and after 6 weeks (zone 1). The increase in zone 1 in the group treated for 1 week was greater than that in the group treated for 6 weeks. This compound-related enhancement of cell proliferation was significantly reversed in the groups allowed to recover. The zonal distribution of increased cell proliferation revealed a selective effect of kresoxim-methyl on hepatocytes in zone 1 (Mellert, Bahnemann & Hildebrand, 1996).

Based on the findings of these studies, it was concluded that the cell proliferating activity of kresoxim-methyl is not influenced by the age of the test animals.

In a study of unscheduled DNA synthesis and S-phase response in rat hepatocytes, groups of three male Wistar (Chbb) rats received kresoxim-methyl (purity 94.3%) in a single oral gavage dose of 0, 20, 200 or 1000 mg/kg bw. 2-Acetylaminofluorene was used as a positive control at a dose of 50 mg/kg bw in the assay of unscheduled DNA synthesis and at 1000 mg/kg bw in the assay of S-phase response. Hepatocytes were prepared by in situ hepatic perfusion 18 hours after treatment. The isolated hepatocytes were cultured with [³H]thymidine for 18 hours, and S-phase response and unscheduled DNA synthesis were evaluated autoradiographically in the labelled cells.

Exposure of rats to kresoxim-methyl in vivo was not cytotoxic to liver cells. Slight but dose-dependent increases in the number of cells in S-phase were observed in all treated groups, with 1% at

0 mg/kg bw, 1.37% at 20 mg/kg bw, 2.78% at 200 mg/kg bw and 2.58% at 1000 mg/kg bw, as well as in the positive control group (5.87%).

The results suggest that kresoxim-methyl induced a moderate increase in S-phase DNA synthesis at 200 mg/kg bw and has a weak potential for enhancing hepatic cell proliferation (Polloth & Hildebrand, 1994c).

Morphology of hepatic proliferation

Groups of three female Wistar (Chbb) rats (12 weeks old) received diets containing kresoxim-methyl (purity 94.3%) at a concentration of 0, 200 or 16 000 ppm (equal to 0, 15 and 1200 mg/kg bw per day, respectively) for 3 weeks. At termination, the livers were fixed in situ by perfusion, and the peroxisomes in the liver were examined by light and electron microscopy after staining with diaminobenzidine to detect catalase activity.

There were no compound-related changes in clinical signs, body weight or feed consumption; reduced body weight gain was observed at 16 000 ppm. No compound-related lesions were observed in the liver, and no difference was seen between treated and control animals in the numbers of peroxisomes.

In view of the above, kresoxim-methyl did not induce peroxisome proliferation under the conditions of this study (Mellert, Kaufmann & Hildebrand, 1995a).

Groups of three female Wistar (Chbb) rats (15 months old) received diets containing kresoxim-methyl (purity 94.3%) at a concentration of 0, 200 or 16 000 ppm (equivalent to 0, 20 and 1600 mg/kg bw per day, respectively) for 3 weeks and were then fixed in situ by perfusion. Liver samples were examined by light and electron microscopy.

There were no compound-related changes in clinical signs or body weight, and no compound-related lesions were observed in the liver on light microscopic examination. Electron microscopy showed that the amount, shape and size of hepatocyte mitochondria in the treated group were comparable with those of controls (Mellert, Kaufmann & Hildebrand, 1995b).

Induction of hepatic metabolic enzyme activities

Groups of 10 male and 10 female Wistar (Chbb:THOM) rats were fed diets containing kresoxim-methyl (purity 94.3%) at a concentration of 0, 200 or 16 000 ppm (equal to 0, 13 and 973 mg/kg bw per day for males and 0, 15 and 1186 mg/kg bw per day for females, respectively) for 3 weeks. The animals were observed for clinical signs, death, body weight and feed consumption. Indicators of hepatic enzymes were measured, including the activities of GGT and drug metabolizing enzymes, the concentration of glutathione in liver homogenates, and the content of cytochrome P450 in microsomes.

Significant increases in the activities of GGT and 7-pentoxoresorufin O-depentyldase and in P450 content were observed in males at 16 000 ppm. The pattern of induction of drug metabolizing enzyme activities resembled that reported for phenobarbital in other studies. In females, only a tendency towards induction was observed (Mellert et al., 1996a).

The above studies are summarized in Table 32.

Table 32. Summary of mechanistic investigations on the carcinogenic mode of action of kresoxim-methyl

Study Doses (Batch / purity)	Results	Reference
Rat foci initiation hepatocarcinogenesis study, single oral gavage 0, 2 388 mg/kg bw (N36 / 94.3%; 26833/147 / 99.4%)	No tumour-initiating activity.	Gamer & Hildebrand (1995a,b)
Rat medium-term promotion hepatocarcinogenesis study, male Fischer rats 0, 200, 800, 8 000, 16 000 ppm (0, 10.78, 42.47, 430.6, 886 mg/kg bw per day) (N112 / 95.4%)	Treatment significantly increased the area (mm ²) and number of DEN-initiated GST-P-positive liver foci per square centimetre at 8 000 and 16 000 ppm. NOAEL = 800 ppm (42.47 mg/kg bw per day)	Harada, Kawakatsu & Nagayoshi (1997)
Rat 3-week S-phase response study, diet, 64-day-old male rats 0, 200, 16 000 ppm (intake not determined; equivalent to 0, 20, 1 600 mg/kg bw per day) (N36 / 94.3%)	Increased S-phase response (BrdU incorporation in DNA) of rat hepatocytes at 16 000 ppm, especially of zone 1 (3-fold increase). No effect at 200 ppm. No effects on body weight, feed intake, clinical parameters or liver histology at 200 or 16 000 ppm, except for slight increase in liver weight at 16 000 ppm.	Polloth & Hildebrand (1994a)
Rat 3-week S-phase response study, diet, male Wistar rats 0, 800, 8 000 ppm (0, 61, 603 mg/kg bw per day) (N36 / 94.9%)	Increased S-phase response in zone 1 hepatocytes at 8 000 ppm, no increased S-phase response at 800 ppm.	Mellert, Bahnmann & Hildebrand (1997)
Rat 3-week S-phase response study, diet; male Wistar rats 0, 200, 16 000 ppm (0, 15, 1 140 mg/kg bw per day) (N36 / 94.3%)	Increased S-phase response (BrdU incorporation in DNA) of rat hepatocytes at 16 000 ppm, especially of zone 1 (3-fold increase). No effect at 200 ppm. No effects on body weight, feed intake, clinical parameters, liver weight or liver histology at 200 or 16 000 ppm.	Polloth & Hildebrand (1994b)
Rat 1-, 6-, 13-week S-phase response, diet, including reversibility, male Wistar rats 0, 16 000 ppm (week 1: 1 660 mg/kg bw per day; week 6: 1 362 mg/kg bw per day; week 13: 1 150 mg/kg bw per day) (N36 / 92.7%)	Enhanced S-phase response over whole 13-week period, peak after 1 week (all three zones affected, with increased liver weight), highest S- phase response in zone 1 after 6- and 13-week treatment; S-phase response was clearly below control values in rats subjected to 2-week or 5- week off-treatment period, after 1-week or 13- week treatment, respectively, indicating counter- regulation of cell proliferation and reversibility.	Mellert, Bahnmann & Hildebrand (1996)
Rat ex vivo UDS / S-phase response Single gavage administration 0, 20, 200, 1 000 mg/kg bw (N36 / 94.3%)	Increased S-phase response at 200 and 1 000 mg/kg bw (no evidence of UDS).	Polloth & Hildebrand (1994c)

Study Doses (Batch / purity)	Results	Reference
Rat 3-week oral diet; electron microscopic investigation of the liver, female Wistar rats 0, 200, 16 000 ppm (0, 15, 1 200 mg/kg bw per day) (N36 / 94.3%)	No induction of peroxisome proliferation.	Mellert, Kaufmann & Hildebrand (1995a)
Rat 3-week oral diet; electron microscopic investigation of liver, 15-month-old Wistar rats 0, 200, 16 000 ppm (intake not determined; equivalent to 0, 20, 1 600 mg/kg bw per day) (N36 / 94.3%)	No changes in mitochondria were noted.	Mellert, Kaufmann & Hildebrand (1995b)
Rat 3-week oral diet; enzyme induction investigation in liver microsomes, male and female Wistar rats 0, 200, 16 000 ppm (males: 0, 13, 973 mg/kg bw per day; females: 0, 15, 1 186 mg/kg bw per day) (N36 / 94.3%)	Significant increase at 16 000 ppm in males for GGT, weak phenobarbital-type enzyme inducer based on slightly increased CYP450 content and PROD activity in males (statistically significant) and females (non-significant). No changes in ω -oxidation of lauric acid, EROD, cyanide-insensitive palmitoyl-CoA oxidation or glutathione content. No substance-related effects at 200 ppm.	Mellert et al. (1996a)

BRdU: 5-bromo-2'-deoxyuridine; bw: body weight; CoA: coenzyme A; CYP450: cytochrome P450; DEN: *N*-nitrosodiethylamine; DNA: deoxyribonucleic acid; EROD: ethoxyresorufin *O*-deethylase; GGT: gamma-glutamyl transferase; GST-P: placental form of glutathione *S*-transferase; ppm: parts per million; PROD: 7-pentoxoresorufin *O*-deethylase; UDS: unscheduled DNA synthesis

(c) *Other special studies*

Mechanism of decreased serum enzyme activities

As marked reductions in the activities of serum ALP and ALT were reported in short- and long-term studies of toxicity in rats, a series of experiments was conducted in which groups of five male and five female rats were fed diets containing kresoxim-methyl at a concentration of 8000 ppm (equivalent to 800 mg/kg bw per day) for 2 weeks.

In the first experiment, ALP activity was determined in serum samples and extracts of liver and small intestine. There was a marked fall in intestinal ALP activity in serum, with no significant change in the contribution of the tissue-nonspecific (liver/bone) isoenzyme. The author indicated that the reduction in serum ALP activity observed in the kresoxim-methyl-treated groups was mostly due to a reduction in the contribution of the intestinal isoenzyme.

In the second experiment, serum ALP activity was markedly reduced after fasting and was increased by feeding a diet supplemented with olive oil. In the third experiment, addition of sera collected from treated animals to sera collected from untreated animals did not suppress ALP activity, indicating the absence of an inhibitor. The observed reduction in serum ALP activity was therefore probably due to a slight alteration in feed absorption in treated rats. These studies did not conform to GLP (Moss, 1994).

In a second study to investigate the reduced enzyme activities, groups of 10 male and 10 female Wistar rats were fed diets containing kresoxim-methyl (purity 94.9%) at a concentration of 0 or 16 000 ppm (equal to 910 mg/kg bw per day for males and 1100 mg/kg bw per day for females) for 2 weeks. The animals were observed for clinical signs, death, body weight and feed consumption. ALT and ALP activities in serum and urine were assayed at the end of the study.

There were no compound-related changes in clinical signs or mortality rates. Statistically significantly decreased feed consumption (about 10% below controls) was observed in treated animals of both sexes. A slight but statistically significant decrease in body weight (2.9% below control value) was observed in treated males. Statistically significantly reduced activities (about 25% compared with the corresponding control value) of ALT and ALP in serum were observed in animals of both sexes treated with 16 000 ppm of the test substance, but no change in the activities of either enzyme in urine was observed. No change in urinary creatinine or urinary volume was observed in treated animals, indicating no change in renal function. Thus, the reduced enzyme activity observed in sera of kresoxim-methyl-treated rats was not caused by a change in renal excretion of the enzymes (Mellert, Decardt & Hildebrand, 1997).

Dietary administration of kresoxim-methyl to rats after repeated pretreatment with dimethoate

In a study to determine whether repeated pretreatment of rats with an organophosphate substantially enhances the toxicity of kresoxim-methyl, a group of three male and three female Wistar rats (main group) and a group of four female rats (satellite group) were treated with dimethoate at a dose of 40 mg/kg bw per day by gavage for 3 days. In the satellite group, cholinesterase activities were monitored.

The administration of dimethoate (40 mg/kg bw per day) for 3 days led to clinical signs of toxicity, such as tremors, lateral position and reduced feed consumption and body weight. The clinical signs observed were expected and are typical for substances inhibiting cholinesterases. After cessation of treatment with dimethoate, all signs were reversible either with or without subsequent treatment with kresoxim-methyl at a dose of 800 or 8000 ppm (equal to 84 and 597 mg/kg bw per day for males and 78 and 605 mg/kg bw per day for females, respectively) for 6 days.

It was observed that repeated pretreatment of rats with dimethoate did not enhance the toxicity of kresoxim-methyl under the conditions of the study. Substantially lowered cholinesterase activities in serum or erythrocytes have therefore no influence on the toxicological profile of kresoxim-methyl (Mellert et al., 1996b).

Effects on the vital functions of animals: general pharmacology

To study the effects of kresoxim-methyl on the vital functions of animals and general pharmacology, the acute effects of kresoxim-methyl on the native behaviour of NMRI mice were investigated at 0.5, 1, 2, 4 and 6 hours after a single oral administration of 1000, 2000 or 5000 mg/kg bw. The behaviour of animals in their home cage as well as in a new environment and their responses to handling were assessed.

At 30 minutes after the administration of the highest dose of kresoxim-methyl, 2/3 mice showed a slight change in their body carriage (hunched posture). However, this finding was also seen in 1/3 mice at 1 hour after treatment with 2000 mg/kg bw and 1/3 mice treated with 1000 mg/kg bw at 2 hours after dosing. In the control group, 2/3 animals administered vehicle only were also recorded to have a hunched posture at 2 hours after treatment. Therefore, this observation is considered not to be related to the test article.

At 4 and 8 hours after treatment, no abnormal findings were recorded in any animals of any group (Dubach-Powell et al., 1994).

(d) *Studies on metabolites*

The data on the acute toxicity and genotoxicity of some metabolites of kresoxim-methyl (Table 33) are presented in Tables 34 and 35. None of the metabolites is more acutely toxic than the parent compound.

Table 33. Identification of metabolites of kresoxim-methyl

Metabolite	Reg. No.	Chemical name
M1	262451	(<i>E</i>)-2-Methoxyimino-2-[2-(<i>o</i> -tolylloxymethyl)phenyl]acetic acid
M2	291685	2-[2(2-Hydroxymethylphenoxy)methyl]phenyl]-2-methoxyiminoacetic acid
M9	292932	2-[2-(4-Hydroxy-2-methylphenoxy)methyl]phenyl]-2-methoxyiminoacetic acid
M15	339774	2-[2-(5-Hydroxy-2-methylphenoxy)methyl]phenyl]-2-methoxyiminoacetic acid

Reg. No.: Registration Number

Table 34. Acute toxicity of some metabolites of kresoxim-methyl

Metabolite	Species	Strain	Sex	Route	LD ₅₀ (mg/kg bw)	Reference
M1	Rat	Chbb Wistar	M + F	Oral	~2 000	Kirsch & Hildebrand (1995)
M2	Rat	Chbb Wistar	M + F	Oral	>5 000	Kirsch & Hildebrand (1994a)
M9	Rat	Chbb Wistar	M + F	Oral	>5 000	Kirsch & Hildebrand (1994b)

bw: body weight; F: female; LD₅₀: median lethal dose; M: male

Table 35. Genotoxicity of some metabolites of kresoxim-methyl

Metabolite	End-point	Test object	Concentration	Results	Reference
M1	Bacterial reverse mutation assay (Ames test)	<i>Salmonella typhimurium</i> strains TA98, TA100, TA1535, TA1537; <i>Escherichia coli</i> strain WP2uvrA; with/without S9 mix	20–5 000 µg/plate (standard plate test) 4–2 500 µg/plate (preincubation test)	Negative	Engelhardt & Hoffmann (1995a)
M1	Syrian hamster embryo cell assay	Syrian golden hamster	7 days: 15–250 µg/mL 24 hours: 100–500 µg/mL	Negative	Engelhardt & Leibold (2005)
M2	Bacterial reverse mutation assay (Ames test)	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537; <i>E. coli</i> strain WP2uvrA; with/without S9 mix	4–5 000 µg/plate (<i>S. typhimurium</i>) 20–5 000 µg/plate (<i>E. coli</i>)	Negative	Engelhardt & Hoffmann (1995b,c)
M9	Bacterial reverse mutation assay (Ames test)	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 (standard plate test); <i>E. coli</i> WP2uvrA	4–5 000 µg/plate (<i>S. typhimurium</i>) 20–5 000 µg/plate (<i>E. coli</i>)	Negative	Engelhardt (1995)

Metabolite	End-point	Test object	Concentration	Results	Reference
M15	Bacterial reverse mutation assay (Ames test)	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 (standard plate test); <i>E. coli</i> WP2uvrA	20–5 000 µg/plate (standard plate test) 4–2 500 µg/plate (preincubation test)	Negative	Engelhardt & Hoffmann (1996)

S9: 9000 × g supernatant fraction from rat liver homogenate

3. Observations in humans

3.1 Medical surveillance on manufacturing plant personnel

All persons handling crop protection products are surveyed by regular medical examinations. There are no specific parameters available for monitoring the effects of kresoxim-methyl. Thus, the medical monitoring programme is designed as a general health check-up, with special interest in the primary target organs presumed to be relevant by analogy from animal experiments. The surveillance programme includes a general physical examination, including neurological status, red and white blood cell counts and liver enzymes. Adverse health effects suspected to be related to kresoxim-methyl exposure have not been observed (BASF, 2018a).

In 1996, a special cross-sectional health examination study of employed men assigned to kresoxim-methyl production was conducted. Personnel at the kresoxim-methyl manufacturing site in Guaratinguetá, Brazil, were examined twice at an interval of 6 months. Employees were subdivided into two main groups: those having no direct contact ($N = 47$) and those with sporadic or daily contact with the final product ($N = 28$). Health end-points of interest were selected based on the results of chronic toxicity studies with animals, which reported indications of liver injury in mice, rats and dogs at high kresoxim-methyl doses. Comparisons of laboratory data were based on analysis of variance and regression analyses incorporating a kresoxim-methyl dose score as the primary explanatory variable and age, smoking history, alcohol intake and body mass index as concomitant variables.

No findings indicative of kresoxim-methyl-induced changes in four liver function indicators (GGT, AST, ALT and ALP) were seen at about 6 months and 1 year after start-up of the manufacturing process. Individual review of health complaints and conditions also did not reveal a connection between any of these occurrences and assignment to the kresoxim-methyl operations. Under the conditions of exposure, which were not quantitatively characterized, there was no evidence of kresoxim-methyl-induced health effects.

The above medical data were compiled by the BASF medical department in April 2008 (BASF, 2018a). Moreover, the personnel who are working with kresoxim-methyl are examined regularly (according to national law). The detailed medical data of persons employed at BASF are covered by data privacy. Adverse health effects have not been observed (BASF, 2018b).

3.2 Direct observation

Some cases of slight irritation of the skin, eyes, mouth or respiratory tract (including rhinitis and cough) have been reported to BASF in persons exposed to kresoxim-methyl in combination with other products. These reports could not be verified, and it is not clear whether kresoxim-methyl was the cause of these irritations (BASF, 2018a).

Data on exposure of the general public to kresoxim-methyl are not available. BASF is not aware of any epidemiological studies performed by third parties (BASF, 2018a). No published literature is available on epidemiological studies or the effect of kresoxim-methyl on humans (BASF, 2018b).

Comments

Biochemical aspects

In rats, orally administered radiolabelled kresoxim-methyl was rapidly, but incompletely, absorbed from the gastrointestinal tract. The extent of oral absorption was about 55–71% at the low dose (50 mg/kg bw) in both sexes, based on recovery of the radiolabel in bile and urine, and 22–28% at the high dose (500 mg/kg bw). Kresoxim-methyl was excreted mainly in the faeces (70% of the low dose and 80% of the high dose), with about 40% excreted via the bile at the low dose and 15% at the high dose within 48 hours. Lesser amounts were excreted in urine (about 20% of the low dose and 10% of the high dose). Peak levels of the radiolabel in plasma were reached 0.5–1 hour after the low dose and 8 hours after the high dose. The plasma half-life of radiolabel was 17–19 hours at the low dose and 22–31 hours at the high dose (Gans & Hildebrand, 1994).

Radioactive material was distributed in all tissues and organs throughout the body, and the total radioactivity in the organs was less than 2% of the administered dose 96 hours after dosing. The highest radioactivity was associated with the gastrointestinal tract, liver and kidney. There was no evidence of accumulation of radioactive material after dosing with ¹⁴C-labelled kresoxim-methyl (Whitby, 1993; Gans, 1995b).

After oral administration in the rat, absorbed kresoxim-methyl was rapidly and completely metabolized. The metabolic pathways of kresoxim-methyl consisted of hydrolytic cleavages of the ester, the oxime ether and the benzyl ether bonds; hydroxylation at the *para* position of the phenoxy ring; oxidation of the aryl-methyl group to benzyl alcohol and its subsequent oxidation to the corresponding carboxylic acid; and conjugation of the resulting hydroxy groups with glucuronate and sulfate. The major metabolites identified in urine and faeces were M1, a hydrolytic product of the acetyl ester; M2, an oxidative metabolite of the aryl-methyl moiety of M1; and M9, a hydroxylated metabolite of the phenoxy ring of M1. M1 and M9 were the major metabolites identified in tissues (Kohl, 1994, 1995, 1998).

Toxicological data

The acute toxicity of kresoxim-methyl in rats was studied by the oral route (LD₅₀ > 2000 mg/kg bw) (Kirsch & Hildebrand, 1993a; Yamamoto, 1994; Cords & Lammer, 2011a), the dermal route (LD₅₀ > 2000 mg/kg bw) (Kirsch & Hildebrand, 1993b; Cords & Lammer, 2011b) and inhalation (LC₅₀ > 263 mg/L air) (Wittmer & Landsiedel, 2011). Kresoxim-methyl is not irritating to the skin of rabbits (Rossbacher, 1992a; Wolf, 2011a) or irritating to the eyes of rabbits (Rossbacher, 1992b; Wolf, 2011b). Kresoxim-methyl is not a skin sensitizer in guinea-pigs in the Magnusson and Kligman maximization test (Rossbacher, 1993) or in the Buehler test (Weiss-Fuchs, 2011).

In repeated-dose toxicity studies in mice, rats and dogs, the predominant target organ was the liver.

In a 28-day range-finding study in mice administered kresoxim-methyl in the diet at a concentration of 0, 500, 2000 or 8000 ppm (equal to 0, 113, 485 and 2141 mg/kg bw per day for males and 0, 182, 798 and 3755 mg/kg bw per day for females, respectively), the NOAEL was 8000 ppm (equal to 2141 mg/kg bw per day), the highest dose tested (Schilling & Hildebrand, 1992a).

In a 3-month study in mice administered kresoxim-methyl in the diet at a concentration of 0, 250, 1000, 4000 or 8000 ppm (equal to 0, 57, 230, 909 and 1937 mg/kg bw per day for males and 0, 80, 326, 1326 and 2583 mg/kg bw per day for females, respectively), the NOAEL was 1000 ppm (equal to 230 mg/kg bw per day), based on decreases in body weight gain (>10%) in males at 4000 ppm (equal to 909 mg/kg bw per day) (Mellert & Hildebrand, 1994a,b).

In a 28-day range-finding study in rats administered kresoxim-methyl in the diet at a concentration of 0, 1000, 4000 or 16 000 ppm (equal to 0, 91, 365 and 1428 mg/kg bw per day for males and 0, 95, 375 and 1481 mg/kg bw per day for females, respectively), the NOAEL was 4000 ppm (equal to 365 mg/kg bw per day), based on the increased serum GGT activity in males, increased albumin

concentration in males and increased relative liver weight in females at 16 000 ppm (equal to 1428 mg/kg bw per day) (Schilling & Hildebrand, 1992b).

In a 90-day study in rats administered kresoxim-methyl in the diet at a concentration of 0, 500, 2000, 8000 or 16 000 ppm (equal to 0, 36, 146, 577 and 1170 mg/kg bw per day for males and 0, 43, 172, 672 and 1374 mg/kg bw per day for females, respectively), the NOAEL was 2000 ppm (equal to 146 mg/kg bw per day), based on decreased body weight and body weight gain and increased GGT activity in males at 8000 ppm (equal to 577 mg/kg bw per day) (Mellert & Hildebrand, 1994c).

In a 90-day study in dogs administered kresoxim-methyl in the diet at a concentration of 0, 1000, 5000 or 25 000 ppm (equal to 0, 30, 150 and 776 mg/kg bw per day for males and 0, 34, 168 and 846 mg/kg bw per day for females, respectively), the NOAEL was 5000 ppm (equal to 150 mg/kg bw per day), on the basis of vomiting and diarrhoea in both sexes and reduced body weight gain in females at 25 000 ppm (equal to 776 mg/kg bw per day) (Mellert & Hildebrand, 1994d).

In a 12-month study in dogs administered kresoxim-methyl in the diet at a concentration of 0, 1000, 5000 or 25 000 ppm (equal to 0, 27, 140 and 710 mg/kg bw per day for males and 0, 30, 150 and 760 mg/kg bw per day for females, respectively), the NOAEL was 5000 ppm (equal to 140 mg/kg bw per day), based on infrequent diarrhoea and vomiting occurring in both sexes and significantly reduced body weights of males at study termination at 25 000 ppm (equal to 710 mg/kg bw per day) (Hellwig & Hildebrand, 1994).

The overall NOAEL for dogs was 5000 ppm (equal to 150 mg/kg bw per day), and the overall lowest-observed-adverse-effect level (LOAEL) was 25 000 ppm (equal to 710 mg/kg bw per day).

In an 18-month assay for carcinogenicity in mice, kresoxim-methyl was administered at a dietary concentration of 0, 400, 2000 or 8000 ppm (equal to 0, 60, 304 and 1305 mg/kg bw per day for males and 0, 81, 400 and 1662 mg/kg bw per day for females, respectively). The NOAEL for toxicity was 2000 ppm (equal to 304 mg/kg bw per day), on the basis of reductions in body weight and body weight gain in both sexes and histopathological changes in the liver and increased liver weights in females at 8000 ppm (equal to 1305 mg/kg bw per day). Kresoxim-methyl was not carcinogenic in mice up to 8000 ppm (equal to 1305 mg/kg bw per day), the highest dose tested (Mellert & Hildebrand, 1994e).

In a 24-month toxicity study in Wistar (Chbb:THOM(SPF)) rats administered kresoxim-methyl in the diet at a concentration of 0, 200, 800, 8000 or 16 000 ppm (equal to 0, 9, 36, 370 and 746 mg/kg bw per day for males and 0, 12, 48, 503 and 985 mg/kg bw per day for females, respectively), the NOAEL for toxicity was 800 ppm (equal to 36 mg/kg bw per day), on the basis of increased activity of serum GGT, increased relative liver weight, and increased incidence and degree of severity of eosinophilic and mixed-cell foci in males at 8000 ppm (equal to 370 mg/kg bw per day). An increased incidence of hepatocellular tumours was observed in both sexes at 8000 ppm (equal to 370 mg/kg bw per day) (Mellert & Hildebrand, 1994f). This study was not powered to characterize the carcinogenic potential of kresoxim-methyl.

In a 24-month study of carcinogenicity in Wistar (Chbb:THOM(SPF)) rats administered kresoxim-methyl at a dietary concentration of 0, 200, 800, 8000 or 16 000 ppm (equal to 0, 9, 36, 375 and 770 mg/kg bw per day for males and 0, 12, 47, 497 and 1046 mg/kg bw per day for females, respectively), the NOAEL for toxicity was 800 ppm (equal to 36 mg/kg bw per day), on the basis of reduced body weight and body weight gain and hepatic alterations at 8000 ppm (equal to 375 mg/kg bw per day). It should be noted that this study was not designed to assess chronic toxicity, and the evaluation of non-neoplastic effects was less thorough than would be required for this purpose. A robust NOAEL for carcinogenicity could not be clearly identified, as the increase in the incidence of hepatocellular tumours in female rats at 800 ppm (equal to 36 mg/kg bw per day) was equivocal, with the incidences varying in the different pathology evaluations performed; clear increases in liver tumours were evident in both sexes at 8000 and 16 000 ppm (Mellert & Hildebrand, 1994g, 1995b,c).

The Meeting concluded that the analysis of the liver tumours produced by kresoxim-methyl in rats was best performed by a benchmark dose (BMD) analysis using the combined tumour incidences in the chronic toxicity study with 20 rats per group (Mellert & Hildebrand, 1994f) and the

carcinogenicity study with 50 rats per group (Mellert & Hildebrand, 1994g). The two studies were performed concurrently in the same laboratory, with the same batch of animals, with no differences in study design that would likely have an impact on the evaluation of liver carcinogenicity. Of the three pathology evaluations performed on these liver tumours, the Meeting concluded that the analysis by the PWG was the most robust and should be utilized for the BMD analysis. The lowest lower limit on the benchmark dose for a 10% response (BMDL₁₀) for liver tumours in female rats identified using “PROASTweb” software was 29.1 mg/kg bw per day, and this was selected as the point of departure for consideration in the risk assessment.

In a limited 24-month carcinogenicity study, kresoxim-methyl was administered to the CrlGlxBrlHan:WI strain of Wistar rats by feed at a concentration of 0 or 16 000 ppm (equal to 0 and 752.1 mg/kg bw per day for males and 0 and 1021.6 mg/kg bw per day for females, respectively). At 16 000 ppm, an increase in liver tumours (hepatocellular adenoma and carcinoma) was observed in both sexes (Kamp et al., 2008).

The Meeting concluded that kresoxim-methyl is carcinogenic in rats, but not in mice.

Kresoxim-methyl was tested for genotoxicity in an adequate range of in vitro and in vivo assays (Engelhardt & Hoffmann, 1993a,b; Hoffmann & Engelhardt, 1993, 1997; Engelhardt & Hildebrand, 1994; Polloth & Hoffmann, 1994a,b,c,d; Honarvar, 2002; Schwindt & Landsiedel, 2008; Schulz & Landsiedel, 2011; Woitkowiak, 2011). No evidence of genotoxicity was found. In the Syrian hamster embryo assay (morphological transformation assay), exposure after 24 hours increased cell transformation only at cytotoxic concentrations (Schwindt & Landsiedel, 2008).

The Meeting concluded that kresoxim-methyl was unlikely to be genotoxic.

A series of mechanistic studies was conducted with kresoxim-methyl, including tests for tumour initiating and promoting potential. In a study on tumour initiating activity, kresoxim-methyl did not increase the number of GST-P-positive hepatocellular foci in rats at a single dose of 2388 mg/kg bw (Gamer & Hildebrand, 1995a,b). In a study on the promoting potential of kresoxim-methyl, rats received an initiating dose of *N*-nitrosodiethylamine and then a diet containing 0, 200, 800, 8000 or 16 000 ppm (equal to 0, 10.78, 42.47, 430.6 and 886 mg/kg bw per day, respectively) of kresoxim-methyl for 6 weeks. The NOAEL for the promoting effect was 800 ppm (equal to 42.47 mg/kg bw per day), based on dose-dependent increases in GST-P-positive hepatocellular foci, indicating a promoting effect of kresoxim-methyl on hepatocarcinogenesis at 8000 ppm (equal to 430.6 mg/kg bw per day) (Harada, Kawakatsu & Nagayoshi, 1997).

Four in vivo studies were conducted to investigate the effect of kresoxim-methyl on hepatic cell proliferation in rat liver by measuring BrdU incorporation into hepatocyte DNA during S-phase DNA synthesis. The overall NOAEL for hepatic cell proliferation was 800 ppm (equal to 61 mg/kg bw per day) (Polloth & Hildebrand, 1994a,b; Mellert, Bahnemann & Hildebrand, 1996, 1997).

Overall, the above mechanistic data support a threshold-based mode of action for carcinogenesis.

Several additional studies were conducted to investigate unscheduled DNA synthesis and S-phase response in rat hepatocytes (Polloth & Hildebrand, 1994c), the morphology of hepatic proliferation in rats (Mellert, Kaufmann & Hildebrand, 1995a), effects on hepatocyte mitochondria (Mellert, Kaufmann & Hildebrand, 1995b), the induction of hepatic metabolic enzyme activities (Mellert et al., 1996a) and the mechanism of decreased serum enzyme activities in rats (Moss, 1994; Mellert, Decardt & Hildebrand, 1997). The Meeting concluded that these studies did not contribute to the risk assessment of kresoxim-methyl.

In view of the lack of genotoxicity, the absence of carcinogenicity in mice and the fact that only hepatocellular tumours were observed and that these were increased in both sexes of rats by a threshold-dependent mode of action, the Meeting concluded that kresoxim-methyl is unlikely to pose a carcinogenic risk to humans from the diet.

In a two-generation study of reproductive toxicity in which rats were fed diets containing kresoxim-methyl at a concentration of 0, 50, 1000, 4000 or 16 000 ppm (equal to 0, 5.1, 102.6, 411.0

and 1623.1 mg/kg bw per day for males and 0, 4.3, 84.3, 348.9 and 1389.3 mg/kg bw per day for females, respectively), the NOAEL for parental toxicity was 1000 ppm (equal to 84.3 mg/kg bw per day), based on reduced body weight and body weight gain, increased serum GGT activity and increased relative kidney weights at 4000 ppm (equal to 348.9 mg/kg bw per day). The NOAEL for reproductive toxicity was 16 000 ppm (equal to 1389.3 mg/kg bw per day), the highest dose tested, as no reproductive effects were observed at any dose. The NOAEL for offspring toxicity was 1000 ppm (equal to 84.3 mg/kg bw per day), based on retarded growth in pups leading to a lower rate of F_{1b} pups per litter with pinna unfolding at 4000 ppm (equal to 348.9 mg/kg bw per day) (Hellwig & Gelbke, 1994a).

In a developmental toxicity study in rats using gavage dosing at 0, 100, 400 or 1000 mg/kg bw per day on days 6–15 of gestation, the NOAEL for maternal toxicity was 1000 mg/kg bw per day, the highest dose tested. The NOAEL for embryo and fetal toxicity was 400 mg/kg bw per day, on the basis of a slight increase in incidence of reduced ossification in fetuses at 1000 mg/kg bw per day (Hellwig & Gelbke, 1994b).

In a developmental toxicity study in rabbits using gavage dosing at 0, 100, 400 or 1000 mg/kg bw per day on days 7–19 of gestation, the NOAEL for maternal and embryo/fetal toxicity was 1000 mg/kg bw per day, the highest dose tested (Hellwig & Hildebrand, 1993).

The Meeting concluded that kresoxim-methyl is not teratogenic in rats or rabbits.

In an acute neurotoxicity study in rats administered a single oral kresoxim-methyl dose of 0, 500, 1000 or 2000 mg/kg bw by gavage, the NOAEL for systemic toxicity and neurotoxicity was 2000 mg/kg bw, the highest dose tested (Mellert, Kaufmann & Hildebrand, 1996a).

In a 90-day study of neurotoxicity in rats given diets containing kresoxim-methyl at a concentration of 0, 1000, 4000 or 16 000 ppm (equal to 0, 72, 292 and 1180 mg/kg bw per day for males and 0, 84, 341 and 1354 mg/kg bw per day for females, respectively), the NOAEL for neurotoxicity was 16 000 ppm (equal to 1180 mg/kg bw per day), the highest dose tested (Mellert, Kaufmann & Hildebrand, 1996b).

The Meeting concluded that kresoxim-methyl is not neurotoxic.

Toxicological data on metabolites and/or degradates

The acute oral toxicity of the rat and plant metabolites M1, M2 and M9 was investigated, and the LD₅₀ was 2000 mg/kg bw or greater for all three metabolites (Kirsch & Hildebrand, 1994a,b, 1995). M1, M2, M9 and M15 are not genotoxic (Engelhardt, 1995; Engelhardt & Hoffmann, 1995a,b,c, 1996; Engelhardt & Leibold, 2005).

M9 is found in urine at over 10% of the dose and is derived from M1, and therefore their toxicity could be considered to be covered by the toxicity of the parent compound.

M2 is present at less than 6% in faeces and urine of rats. For chronic toxicity, the threshold of toxicological concern (TTC) approach (Cramer class III) could be applied for M2 and its conjugate, expressed as M2.

Human data

No adverse health effects suspected to be related to kresoxim-methyl exposure have been observed in persons handling crop protection products.

In reports on manufacturing plant personnel, no adverse health effects were noted (BASF, 2018a).

No information on accidental or intentional poisoning in humans was identified.

No epidemiological studies are available (BASF, 2018a,b).

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

Toxicological evaluation

The Meeting established an ADI of 0–0.3 mg/kg bw, derived from a BMDL₁₀ of 29.1 mg/kg bw per day from the 2-year chronic toxicity and carcinogenicity studies in rats, on the basis of liver tumours produced by a threshold-based mode of action. A safety factor of 100 was applied.

The Meeting concluded that the ADI could be applied to the metabolites M1 and M9 and their conjugates.

The Meeting concluded that it was not necessary to establish an ARfD for kresoxim-methyl in view of its low acute oral toxicity and the absence of any other toxicological effects, including developmental toxicity, that would be likely to be elicited by a single dose.

Levels relevant to risk assessment of kresoxim-methyl

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity ^a	Toxicity	2 000 ppm, equal to 304 mg/kg bw per day	8 000 ppm, equal to 1 305 mg/kg bw per day
		Carcinogenicity	8 000 ppm, equal to 1 305 mg/kg bw per day ^b	–
Rat	Two-year study of toxicity ^a	Toxicity	800 ppm, equal to 36 mg/kg bw per day	8 000 ppm, equal to 370 mg/kg bw per day
	Two-year study of carcinogenicity ^a	Toxicity	800 ppm, equal to 36 mg/kg bw per day	8 000 ppm, equal to 375 mg/kg bw per day
		Carcinogenicity	29.1 mg/kg bw per day (BMDL ₁₀)	–
	Two-generation study of reproductive toxicity ^a	Reproductive toxicity	16 000 ppm, equal to 1389.3 mg/kg bw per day ^b	–
		Parental toxicity	1 000 ppm, equal to 84.3 mg/kg bw per day	4 000 ppm, equal to 348.9 mg/kg bw per day
		Offspring toxicity	1 000 ppm, equal to 84.3 mg/kg bw per day	4 000 ppm, equal to 348.9 mg/kg bw per day
	Developmental toxicity study ^c	Maternal toxicity	1 000 mg/kg bw per day ^b	–
		Embryo and fetal toxicity	400 mg/kg bw per day	1 000 mg/kg bw per day
	Acute neurotoxicity study ^c	Neurotoxicity	2 000 mg/kg bw ^b	–
	Ninety-day neurotoxicity study ^a	Neurotoxicity	1 180 mg/kg bw per day ^b	–

Species	Study	Effect	NOAEL	LOAEL
Rabbit	Developmental toxicity study ^c	Maternal toxicity	1 000 mg/kg bw per day ^b	–
		Embryo and fetal toxicity	1 000 mg/kg bw per day ^b	–
Dog	Ninety-day and 1-year studies of toxicity ^{a,d}	Toxicity	5 000 ppm, equal to 150 mg/kg bw per day	25 000 ppm, equal to 710 mg/kg bw per day

^a Dietary administration.

^b Highest dose tested.

^c Gavage administration.

^d Two or more studies combined.

Acceptable daily intake (ADI) (applies to kresoxim-methyl, M1 and M9 and their conjugates, expressed as kresoxim-methyl)

0–0.3 mg/kg bw

Acute reference dose (ARfD)

Unnecessary

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

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

Critical end-points for setting guidance values for exposure to kresoxim-methyl

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	Rapidly, but incompletely, absorbed (~60%)
Dermal absorption	No data
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	In faeces (70% of the low dose and 80% of the high dose); in urine (about 20% of the low dose and 10% of the high dose)
Metabolism in animals	Extensive
Toxicologically significant compounds in animals and plants	Kresoxim-methyl

Acute toxicity

Rat, LD ₅₀ , oral	>2 000 mg/kg bw
Rat, LD ₅₀ , dermal	>2 000 mg/kg bw
Rat, LC ₅₀ , inhalation	>5.263 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Guinea-pig, dermal sensitization	Not sensitizing (Buehler & maximization)

<i>Short-term studies of toxicity</i>	
Target/critical effect	Diarrhoea, vomiting, reduced body weight gain
Lowest relevant oral NOAEL	150 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day, highest dose tested (rat)
Lowest relevant inhalation NOAEC	No data
<i>Long-term studies of toxicity and carcinogenicity</i>	
Target/critical effect	Liver; hepatotoxicity and tumours (rat)
Lowest relevant BMDL ₁₀	29.1 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice, carcinogenic in rats ^a
<i>Genotoxicity</i>	
	No evidence of genotoxicity in vitro or in vivo ^a
<i>Reproductive toxicity</i>	
Target/critical effect	No reproductive effects
Lowest relevant parental NOAEL	84.3 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	84.3 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	1 389.3 mg/kg bw per day, highest dose tested (rat)
<i>Developmental toxicity</i>	
Target/critical effect	Reduced ossification (rat)
Lowest relevant maternal NOAEL	1 000 mg/kg bw per day, highest dose tested (rat and rabbit)
Lowest relevant embryo/fetal NOAEL	400 mg/kg bw per day (rat)
<i>Neurotoxicity</i>	
Acute neurotoxicity NOAEL	2 000 mg/kg bw, highest dose tested (rat)
Subchronic neurotoxicity NOAEL	1 180 mg/kg bw per day, highest dose tested (rat)
Developmental neurotoxicity NOAEL	No data

^a Unlikely to pose a carcinogenic risk to humans from the diet.

Summary

	Value	Study	Safety factor
ADI	0–0.3 mg/kg bw ^a	Two-year chronic toxicity and carcinogenicity studies in rats	100
ARfD	Unnecessary	–	–

^a Applies to kresoxim-methyl, M1 and M9 and their conjugates, expressed as kresoxim-methyl.

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