Behaviour of Fluoxastrobin (HEC 5725) in plants and animals

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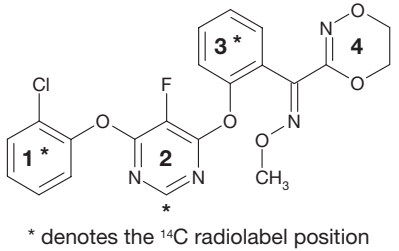
1 Introduction

Fluoxastrobin (HEC 5725) is a newly developed fungicide for use in a variety of cereals and various field crops. The behaviour (metabolism) of this methoxyacrylate fungicide was investigated in plant and animal studies using a radiolabelled parent compound. The metabolism studies were essential for the identification of degradation products, the elucidation of the metabolic pathways, the development of analytical methods, the enforcement of maximum residue limits (MRL's) and the dietary risk assessment. The article is divided in three sections describing the metabolism in the relevant crops, in rats as a part of the toxicological data package and in the farm animals, i.e. lactating goat and laying hens. The studies were conducted using three different radioactive labels (synthesis by BCS-R-PT, Wuppertal) as shown below:

For the sake of clarity, all information given in the following text and in tables focuses on the total amount of identified and characterised compounds. The numerous metabolites were grouped by the rings or fragments of rings they still contained (e.g. metabolites containing ring 3 and ring 4 were abbreviated as "3,4" in tables, or metabolites containing rings 2, 3 and 4 were abbreviated as "2,3,4").

2 Behaviour in plants

Results of the metabolism in plants are described for spring wheat (Stork, 2001 a-c), tomatoes (Reiner, 2001 a-b) and confined rotational crops (Neumann, 2001 a-c). The applied active substance was a mixture of the E- and Z-isomer at a ratio of about 98/2 or 97/3 corresponding to the fluoxastrobin formulations in agricultural practice. The quantitation of the parent compound and of the meta-



* denotes the ^{14}C radiolabel position

ring 1-label = [chlorophenyl-UL-^{14}C]HEC 5725

ring 2-label = [pyrimidine-2-^{14}C]HEC 5725

ring 3-label = [methoxyiminotolyl-ring-UL-^{14}C]HEC 5725

bolites in the tables is expressed as percent of the TRR (total radioactive residue) and as mg/kg parent compound equivalents.

2.1 Metabolism in spring wheat

Methodology:

The wheat studies (3 labels) were each conducted with a seed dressing (FS 200 formulation, 55 g a.s./ha) followed by two spray applications (EC 100 formulation, each at 300 g a.s./ha at BBCH stages 32 and 69) using 1 m² planting containers. The three studies simulated the intended agricultural use of 655 g a.s./ha calculated from the seed treatment and up to three spray applications (each at 200 g a.s./ha) in agricultural practice. Forage, hay, straw and grain were sampled. The extraction was conducted with acetonitrile/water mixtures. For analysis, the radioactivity was partitioned into an organic phase (dichloromethane) and an aqueous phase. Relevant solid residues were further investigated following chemical or enzymatic extraction procedures. The metabolites were quantified and analysed by radio-HPLC, and UV-detectors were used for co-chromatography with reference compounds. Radioactivity of liquid samples was measured by LSC (Liquid Scintillation Counting). Radioactivity of solids was determined following combustion and absorption of $^{14}CO_2$ in a specific scintillator liquid.

Findings:

In forage, the TRR's were relatively low (0.02 to 0.06 mg/kg) because the plants had been exposed to the seed treatment only. The highest residues (74.7 to 80.0 mg/kg) were observed in straw at maturity reflecting a worst case scenario following spray applications, because the residues were protected against wash-off by rain in the vegetation hall and in the greenhouse. Straw was the most impor-

Table 1: Fluoxastrobin and metabolites in spring wheat straw

Radiolabel	ring 1-label		ring 2-label		ring 3-label	
	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg
Fluoxastrobin (parent compound)	79.9	62.42	72.8	54.34	72.3	57.81
1,2,3,4	9.8	7.64	11.1	8.31	11.0	8.79
2,3,4	–	–	3.2	2.39	3.8	3.04
1,2	0.6	0.43	1.0	0.74	–	–
3,4	–	–	–	–	0.8	0.66
1	3.3	2.57	–	–	–	–
Sum identified	93.5	73.05	88.1	65.78	87.9	70.31
Characterised*	3.3	2.59	10.5	7.81	9.9	7.95
Subtotal identified and characterised	96.8	75.65	98.5	73.59	97.9	78.26
Non-extractable residue	3.2	2.5	1.5	1.09	2.1	1.69
Total	**100**	**78.14**	**100**	**74.68**	**100**	**79.95**

* Non-identified metabolites, characterised by extraction procedure and partitioning (DCM, H_2O phase) or exhaustive extraction (microwave extract), followed by HPLC chromatography.

Table 2: Fluoxastrobin and metabolites in spring wheat grain

Radiolabel	ring 1-label		ring 2-label		ring 3-label	
	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg
Fluoxastrobin (parent compound)	86.0	0.45	51.6	0.30	63.0	0.45
1,2,3,4	4.2	0.02	3.2	0.02	4.7	0.03
2,3,4	–	–	3.0	0.02	5.0	0.04
1	1.2	0.01	–	–	–	–
Carbohydrates (natural products)	–	–	17.1	0.10	–	–
Sum identified	91.5	0.48	75.0	0.43	72.7	0.51
Characterised*	2.1	0.01	19.4	0.11	22.9	0.16
Subtotal identified and characterised	93.6	0.49	94.4	0.54	95.6	0.67
Non-extractable residue	6.4	0.03	5.7	0.03	4.4	0.03
Total	**100**	**0.53**	**100**	**0.57**	**100**	**0.71**

* Non-identified metabolites, characterised by extraction procedure and partitioning (DCM, H_2O phase) or exhaustive extraction (enzymatic treatment), followed by HPLC chromatography.

tant plant material for the isolation and identification of metabolites. The TRR's in grain were significantly lower and ranged from 0.53 to 0.71 mg/kg.

In total, about 93-99 % of the TRR was either identified or characterised in each RAC (raw agricultural commodity). About 1-6 % of the TRR remained unextracted in the solids, and was not further investigated.

As an example, the quantitation of metabolite groups (see explanations of metabolite groups based on ring systems in the introduction) is shown for straw (Table 1) and grain (Table 2).

The numerous identified structures in different matrices of plant and animal samples are shown in a common proposed metabolic pathway (Figure 3).

The investigation of the nature of the residue revealed that the TRR in hay, straw, and grain consisted mainly of unchanged parent compound (52-88 %). Forage, which was exposed to a seed treatment only, contained less parent compound (22-27 % of the TRR) on a very low absolute level (TRR $\leq$0.01 mg/kg).

Despite of the generally high amounts of parent compound, the metabolism of fluoxastrobin revealed a very complex pattern in spring wheat, and a total of 37 metabolites was identified. Most of these metabolites contained all four rings or at least three rings plus fragments of the dioxazine ring (ring 4). In addition to the identified substances, numerous minor metabolites or metabolite groups (most of them far below 1 % of the TRR) were characterised by the extraction procedure, partitioning behaviour and retention time in an optimised HPLC analytical system.

2.2 Metabolism in tomatoes

Methodology:

The tomato plants were sprayed three times with fluoxastrobin (SC 360 formulation, each at 144 g a.s./ha, 432 g a.s./ha in total) using only two labels (ring 1-

label and ring 3-label) because they were the most efficient ones for the elucidation of the metabolism in crops as was concluded from the results in wheat. The metabolism studies simulated an intended use pattern of up to four spray applications at 108 g a.s./ha each amounting to 432 g a.s./ha in total. The tomato plants were cultivated in a greenhouse.

The first spray application was conducted when small tomatoes were visible. The second spray application was 14 days later when the majority of the fruit had reached about 50 % of their final size and the third spray application was performed when about 30 % of the fruit showed the typical ripe colour (17 days after the second application). Tomato fruits were harvested three days after the final treatment. Red and slightly red tomatoes were rinsed with methanol, and both fruits and surface wash solution were analysed.

Findings:

The TRR in the harvested tomatoes amounted to 0.418 mg/kg (ring 1-label) and 0.635 mg/kg (ring 3-label). The main portion of the TRR was found in the surface wash solution (91.1-91.5 %). The part of the TRR found inside the tomato fruit proved to be almost completely extractable (8.2-8.7 %). Thus in total, about 99.8 % of the TRR was extracted, and only 0.2 % remained unextracted in the solids. Parent compound and 4 metabolites were identified. Unchanged fluoxastrobin clearly constituted the main component and represented about 98 % of the TRR.

Several minor metabolites were characterised by the extraction procedure and retention time in the optimised HPLC analytical system. The results of the two metabolism studies on fluoxastrobin in tomatoes are summarised in Table 3.

2.3 Metabolism in confined rotational crops

Methodology:

Additionally, the behaviour of fluoxastrobin was investigated for representative crop groups in confined rotational

Table 3: Fluoxastrobin and metabolites in tomato fruits

Radiolabel	ring 1-label		ring 3-label	
	% of TRR	mg/kg	% of TRR	mg/kg
Fluoxastrobin (parent compound)	98.0	0.410	98.0	0.622
1,2,3,4	0.3	0.001	0.4	0.003
1,2	0.4	0.002	-	-
3,4	-	-	0.3	0.002
Sum identified	98.7	0.413	98.7	0.627
Characterised*	1.0	0.004	1.1	0.007
Subtotal identified and characterised	99.8	0.417	99.8	0.634
Non-extractable residue	0.2	0.001	0.2	0.001
Total	**100**	**0.418**	**100**	**0.635**

* Non-identified metabolites, characterised by extraction procedure and HPLC chromatography. Several compounds were characterised; each of them was ≤ 0.002 mg/kg.

crop studies (3 labels) after root uptake of parent compound and soil metabolites. Fluoxastrobin was sprayed onto the soil of 1 m² planting containers (846 g a.s./ha for ring 1-label, 841.5 g a.s./ha for ring 2-label, and 683 g a.s./ha for ring 3-label). The differences in the applied amount reflected the maximum annual amount in agricultural practice in relevant target crops when the respective study was started. Spring wheat (cereal, small grain), Swiss chard (leafy crop) and turnips (root crop) were sown after 30 days and grown to maturity. The same crops were again cultivated when the harvest of crops of the first rotation was completed, and a third time after finishing the second rotation. Seven plant samples (wheat forage, wheat hay, wheat straw, wheat grain, Swiss chard, turnip leaves and turnip roots) were extracted and analysed for each rotation for all labels. Plants were grown in the greenhouse or in the vegetation hall of the Bayer testing facility.

Table 4: Total radioactive residues in rotational crops grown in soil treated with fluoxastrobin

Crop	Sample material	Rotation	Total radioactive residues in parent compound equivalents (mg/kg)		
			Radiolabel		
			ring 1-label	ring 2-label	ring 3-label
Wheat	Forage	First	0.10	0.12	0.17
		Second	0.11	0.20	0.11
		Third	0.05	0.18	0.23
	Hay	First	2.03	0.71	0.50
		Second	0.31	1.07	0.54
		Third	0.18	0.55	0.37
	Straw	First	2.38	2.44	1.41
		Second	1.10	1.72	1.31
		Third	0.21	0.75	0.56
	Grain	First	0.04	0.11	0.04
		Second	0.03	0.13	0.04
		Third	0.04	0.07	0.03
Swiss chard	Leaves	First	0.19	0.16	0.08
		Second	0.15	0.11	0.07
		Third	0.04	0.14	0.06
Turnip	Leaves	First	0.06	0.06	0.02
		Second	0.06	0.05	0.03
		Third	0.01	0.06	0.02
	Roots	First	0.03	0.03	0.01
		Second	0.03	0.02	0.01
		Third	0.01	0.01	0.01

Findings:

The total radioactive residue was low in all crops of all rotations (table) and ranged from 0.01-2.44 mg/kg. Differentiating the level of TRR by sample materials, it was generally highest in wheat straw and hay and lowest in turnip roots and leaves. In the three different studies, the following ranges of TRR were determined:

- First rotation:
  0.03-2.38 mg/kg (ring 1-label),
  0.03-2.44 mg/kg (ring 2-label),
  0.01-1.41 mg/kg (ring 3-label),
- Second rotation:
  0.03-1.10 mg/kg (ring 1-label),
  0.02-1.72 mg/kg (ring 2-label),
  0.01-1.31 mg/kg (ring 3-label),
- Third rotation:
  0.01-0.21 mg/kg (ring 1-label),
  0.01-0.75 mg/kg (ring 2-label),
  0.01-0.56 mg/kg (ring 3-label).

Comparing the results from the three rotations (Table 4), a decline from the first to the third rotation was noticeable for the commodities with the highest amount of TRR, i.e. especially for wheat straw and also for wheat hay. In all other commodities, the TRR was very low to begin with and

varied around that low level for all three rotations (0.01-0.06 mg/kg for turnip commodities, 0.03-0.13 mg/kg for wheat grain, and 0.04-0.23 mg/kg for wheat forage and Swiss chard leaves.
The metabolic pattern observed for fluoxastrobin in succeeding crops was well comparable for all tested crops and for all three rotational crop studies.
As an example, the quantitation of metabolite groups of straw is shown in Table 5 - Table 7.

Table 5: Fluoxastrobin and metabolites in wheat straw of the confined rotational crop study conducted with ring 1-label

Compound / Rotation	First rotation		Second rotation		Third rotation	
	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg
Fluoxastrobin (parent compound)	49.5	1.18	35.6	0.39	26.3	0.06
1,2,3,4	24.8	0.58	26.8	0.29	27.8	0.06
1	7.0	0.17	19.4	0.21	16.3	0.03
Sum identified	81.3	1.93	81.8	0.90	70.4	0.15
Characterised*	15.1	0.36	9.6	0.11	15.9	0.03
Subtotal identified and characterised	96.4	2.29	91.4	1.00	86.3	0.18
Non-extractable residue	3.6	0.09	8.7	0.10	13.7	0.03
Total	**100**	**2.38**	**100**	**1.10**	**100**	**0.21**

* Metabolites were characterised by extraction behaviour, phase partitioning and chromatographic behaviour, each of them amounted to <0.03 mg/kg

Table 6: Fluoxastrobin and metabolites in wheat straw of the confined rotational crop study conducted with ring 2-label

Compound / Rotation	First rotation		Second rotation		Third rotation	
	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg
Fluoxastrobin (parent compound)	22.1	0.54	26.0	0.45	7.4	0.06
1,2,3,4	33.2	0.81	18.1	0.31	6.5	0.05
2,3,4	22.4	0.55	23.2	0.40	43.3	0.33
1,2	1.3	0.03	n.d.*	n.d.*	n.d.*	n.d.*
Sum identified	78.9	1.93	67.4	1.16	57.2	0.43
Characterised*	16.5	0.40	25.4	0.44	30.4	0.23
Subtotal identified and characterised	95.4	2.33	92.9	1.6	87.6	0.66
Non-extractable residue	4.6	0.11	7.2	0.12	12.4	0.09
Total	**100**	**2.44**	**100**	**1.72**	**100**	**0.75**

n.d.* Not detected or not further analysed due to very low residues (<0.01 mg/kg)

** Metabolites were characterised by extraction behaviour, phase partitioning and chromatographic behaviour, each of them amounted to <0.09 mg/kg

Table 7: Fluoxastrobin and metabolites in wheat straw of the confined rotational crop study conducted with ring 3-label

Compound / Rotation	First rotation		Second rotation		Third rotation	
	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg
Fluoxastrobin (parent compound)	28.0	0.40	26.2	0.34	21.9	0.12
1,2,3,4	37.6	0.53	29.1	0.38	21.8	0.12
2,3,4	15.3	0.22	14.1	0.18	23.2	0.13
3,4	0.8	0.01	0.6	0.01	0.9	0.01
Sum identified	81.7	1.15	69.9	0.92	67.8	0.38
Characterised *	12.0	0.17	23.6	0.31	22.8	0.13
Subtotal identified and characterised	93.7	1.32	93.6	1.23	90.6	0.51
Non-extractable residue	6.3	0.09	6.4	0.08	9.3	0.05
Total	**100**	**1.41**	**100**	**1.31**	**100**	**0.56**

* Metabolites were characterised by extraction behaviour, phase partitioning and chromatographic behaviour, each of them amounted to <0.09 mg/kg

3 Behaviour in animals

3.1 Biokinetics and metabolism in the rat

The biokinetic behaviour and metabolism was studied in the rat (Klempner, 2001 and 2002, and Neumann, 2001d) using fluoxastrobin with the ^{14}C radiolabel in ring 1, ring 2 and ring 3. Quantitative whole body-autoradiography (QWBA) studies were also conducted to describe the distribution kinetics of the total radioactivity in the various organs and tissues of the rat (Neumann and Weber, 2001a and b, and Neumann and Weber, 2002).

3.1.1 Absorption, distribution and excretion

Methodology:

Groups of young adult male and female Wistar rats were given a single oral dose of the test compound, as a suspension in 0.5 % aqueous tragacanth, according to the following treatment and sampling schedule (Table 8).

Samples for analysis of radioactivity were collected separately from each animal. Blood was separated into plasma and red blood cells. Skin, gastrointestinal tract, organs, tissues and the residual carcass were weighed immediately after dissection, lyophilised and homogenised. Aliquots were withdrawn for determination of radioactivity by combustion. Adrenals, thyroids, ovaries, renal fat and uterus were dissolved in a tissue solubiliser prior to the determination of radioactivity by direct scintillation counting. All other solid tissue samples were combusted in an oxygen atmosphere, the $^{14}CO_2$ was trapped and subjected to liquid scintillation counting (LSC). Biokinetic parameters were calculated from the total radioactivity measured in plasma samples.

Table 8: Survey of the rat metabolism experiments

Test no.	^{14}C label position	No. and sex of animals	Dose level and route	Duration (hours)	Sample material	Sample intervals (hours post administration)
A1	Ring 1	4 males	1 mg/kg oral	48	expired air	4, 8, 24, 48, (72)
A2	Ring 2			(A1-A2)	urine	4, 8, 24, 48, (72)
A3	Ring 3			72 (A3)	faeces	24, 48, (72)
					GIT, skin, carcass	48 or 72 (at sacrifice)
B1	Ring 1	4 males	1 mg/kg oral	48	plasma	10, 20, 40, 60, 90 min., 2, 3, 4, 6, 8, 24, 32, 48 h
B2	Ring 2					
B3	Ring 3				urine	4, 8, 24, 48
C	Ring 3	4 females			faeces,	24, 48
					tissues, organs, carcass	48 (at sacrifice)
D	Ring 3	4 males	100 mg/kg	48 oral	plasma	5, 10, 20, 40, 60, 90 min., 2, 3, 4, 6, 8, 24, 32, 48 h
E	Ring 3	4 females			urine	4, 8, 24, 48
					faeces	24, 48
					tissues, organs, GIT, skin, carcass	48 (at sacrifice)
F	Ring 3	4 males	1 mg/kg oral; repeated dose test (14 x unlabelled and 1 x 14c-labelled)	48	plasma	5, 10, 20, 40, 60, 90 min., 2, 3, 4, 6, 8, 24, 32, 48 h
G	Ring 3	4 females			urine	4, 8, 24, 48
					faeces	24, 48
					tissues, organs, GIT, skin, carcass	48 (at sacrifice)
H1	Ring 1	4 males	1 mg/kg oral; bile-duct cannulation experiment	30	bile	4, 8, 24, (30)
H3	Ring 3			24	urine	4, 8, 24, (30)
					faeces	24, (30)
					GIT, skin, carcass	24 or 30 (at sacrifice)
I1	Ring 1	5 or 8 males	3 mg/kg oral; (QWBA)	168 (I1, I2, J1, J2)	urine	1, 4, 8, 24, 48, 72, 96, 120, 144, 168 in dependence of the time of sacrifice
I2	Ring 2					
I3	Ring 3					
J1	Ring 1	5 or 8 females		48 (I3, J3)	faeces	24, 48, 72, 96, 120, 144, 168 in dependence of the time of sacrifice
J2	Ring 2					
J3	Ring 3					
					whole body as well as tissues and organs	1, 4, 8, 24, 48, 72, 120, 168 (time of sacrifice for 1 animal, each)

Curve-fitting software (TOPFIT v.2) was used to calculate biokinetic parameters by plasma curve analysis. The standard 2- or 3-compartment model was applied for curve fitting computations.

Findings:

Absorption

Fluoxastrobin was rapidly and completely absorbed from the gastrointestinal tract (GIT) of rats. In all tests, maximum plasma concentrations were reached at 0.2-8 hours after administration.

The degree of absorption was determined by two bile-duct cannulation experiments (H1, H3). The major portion, about 77 or 87 % of the dose was excreted via the bile, 3 or 5 % in the urine and 11 % in the faeces. The rate of biliary and renal excretion together amounts to about 80 or 92 %. Together with the amount that remained in the carcasses (4 or 6 %), it can be concluded that the administered dose was nearly quantitatively absorbed. The considerable amount of radioactivity found in the bile and faeces was a proof for a significant enterohepatic circulation process between the small intestine and liver. The fact that no parent compound was detected in the bile fluid indicates a definite first pass effect in the liver.

Distribution

The administered radioactivity was rapidly distributed to all tissues after oral administration of fluoxastrobin. This is visualised exemplarily in the whole-body autoradiogram in Figure 1 and quantitatively in Figure 2. Thereafter, all tissue concentrations declined rapidly and at 48 hours all tissue concentrations were close to, or below, the limit of quantification. The highest concentrations of radioactivity were always detected in the organs and tissues responsible for metabolism and excretion, i.e. in liver, kidneys, and urinary bladder as well as in the gastro intestinal tract. The radioactivity remaining in the body including the gastrointestinal tract at sacrifice (48 hours) was generally low. It amounted to about 1 % of the dose in the tests with the ring 1- and ring 2-label of fluoxastrobin (B1, B2), and to 0.3 - 0.7% in the low-, high- and multiple-dose experiments with the ring 3-label.

Comparing the results obtained for the 3 different labels of fluoxastrobin, the concentration of residues in many tissues are by a factor of 2-5 higher for the ring 1- and ring 2-label than for the ring 3-label. This is most likely caused by a different distribution and excretion behaviour of the different label specific metabolites.

However, irrespective of label, dose and sex of the test animal, no accumulation of fluoxastrobin-related residues was observed. The following conclusions were drawn from all rat studies:

- fast absorption of the radioactivity from the gastrointestinal tract,
- fast distribution of the radioactivity within the blood and most organs and tissues of the body with a strong preference to the excretory and metabolising organs like liver and kidneys,
- low concentrations of radioactivity in glandular organs or tissues, which are involved in the regulation of hormones (e.g. adrenal and thyroid gland, ovary and uterus of female rats or testes of male rats),
- low concentrations of radioactivity in brain and spinal cord,
- significant decline of concentrations within time in all organs and tissues of male and female rats,

- concentrations of radioactivity of less than the limit of quantitation or even less than the limit of detection in most organs and tissues of male and female rats at test termination (48 or 168 hours after dosing),
- no long-lasting retention of radioactivity in specific organs or tissues,
- similar distribution pattern of radioactivity in male and female rats.

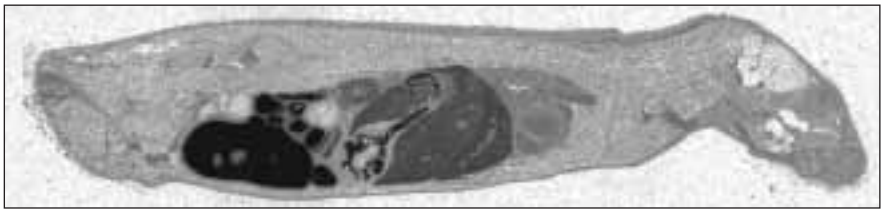


Fig. 1: Whole body radioluminogram showing the distribution of radioactivity in organs and tissues of the rat 4 hours after oral administration of [chlorophenyl-UL-^{14}C]fluoxastrobin

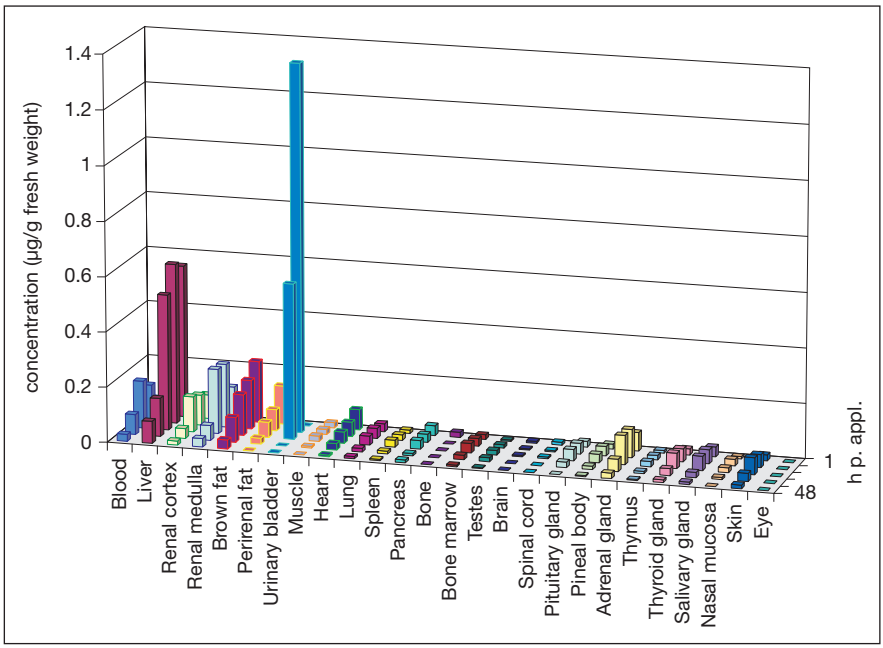


Fig. 2: Total radioactive residues after oral administration of [chlorophenyl-UL-^{14}C]fluoxastrobin at a rate of 3 mg/kg body weight

Excretion

The expiration tests (A1-A3) revealed that only a minor percentage (0.02-0.24 % during 48 hours) of the administered dose was expired via the air.

The major route of elimination was biliary and therefore faecal. Already, within 48 hours after dosing, about 70-90 % of the total administered dose was excreted in faeces, and only 11-20 % in urine. Hence, excretion of fluoxastrobin related residues occurred fast and at a high rate (Table 9).

3.1.2 Metabolism

Methodology:

Urine and bile samples as well as faecal extracts were analysed by radio-HPLC. All major metabolites were quantified and then identified by HPLC co-chromatography with reference compounds using two independent optimised chromatographic methods with different selectivity. Prominent metabolites in bile, urine and faeces were isolated by micropreparative HPLC and identified by LC-MS/MS.

Findings:

In the rat, parent compound was found in small quantities only. It accounted for <1 - 8.3 % of the administered dose with the exception of the two high dose experiments (D, E). There the percentage of the unchanged parent compound accounted for about 43 % (female rats) and 54 % (male rats) of the dose.

Table 9: Cumulative excretion of fluoxastrobin

Test no.	Label	Dose mg/kg bw	Sex	T [hours]	Urine %	Faeces %	Bile %	Sub-total %	Body %	Total %
A1	1	1	M	48	13.6	77.0	–	90.9	1.5	92.4
A2	2	1	M	48	12.1	73.3	–	85.5	1.3	86.8
A3	3	1	M	72	16.9	80.3	–	97.3	0.3	97.6
B1	1	1	M	48	13.2	76.4	–	89.6	1.8	91.4
B2	2	1	M	48	12.0	71.7	–	83.6	1.2	84.9
B3	3	1	M	48	20.0	84.7	–	104.7	0.7	105.5
C	3	1	F	48	20.2	70.4	–	90.6	0.5	91.1
D	3	100	M	48	15.0	91.1	–	106.0	0.3	106.3
E	3	100	F	48	11.0	86.4	–	97.4	0.4	97.7
F	3	15 x 1	M	48	19.4	74.1	–	93.6	0.7	94.3
G	3	15 x 1	M	48	18.5	78.1	–	96.6	0.4	97.0
H1	1	1	M	30	3.2	11.3	77.3	91.9	6.4	98.3
H3	3	1	M	24	4.8	10.6	87.4	102.8	3.8	106.6
I1	1	3	M	168	15.6	86.4	–	102.0	–	–
I2	2	3	M	168	10.6	98.8	–	109.4	–	–
I3	3	3	M	48	18.8	77.0	–	95.8	–	–
J1	1	3	F	168	12.4	87.0	–	99.5	–	–
J2	2	3	F	168	15.7	94.3	–	110.0	–	–
J3	3	3	F	48	17.5	80.0	–	97.5	–	–

M = male, F = female, T= test duration

In rats, fluoxastrobin was degraded extensively and in total 51 metabolites were identified (Table 10). About 53-90 % of the total administered dose were identified. Furthermore, 8-28 % were characterised by the HPLC elution behaviour. In two experiments conducted with ring 1-radiolabel (B1, H1), an additional polar peak region accounted for 6-9 % of the total administered dose. In total, the rate of identification and characterisation was high for all experiments.

Metabolites, which still contained all 4 rings or rings 1,2,3 and fragments of ring 4, always represented the largest group of metabolites (about 12-45 % of the total administered dose). In the bile, most of the metabolites were various hydroxy, hydroxy-methoxy and multiple-hydroxy metabolites of fluoxastrobin conjugated with glucuronic acid. The corresponding non-conjugated aglyca were found mostly in faeces.

Cleavage of the chlorophenyl moiety of fluoxastrobin led to the des-chlorophenyl metabolites (2,3,4 ring metabolites), of which HEC 5725-des-chlorophenyl and HEC 5725-des-chlorophenyl-dioxazine-OH are the most important ones (8-15 % and 3-14 % of the total administered dose, respectively).

Cleavage of the ether bridge between the pyrimidine ring and the methoxyimino-tolyl ring of fluoxastrobin ended in 1,2 ring metabolites (about 5-10 % of the dose). Metabolites of this group are HEC 5725-phenoxy-hydroxypyrimidine, HEC 5725-4-OH-pyrimidine-OH and its conjugates.

Table 10: Metabolite identification and quantification

Test no.	B1	H1	A2	B2	A3	B3	C	D	E	F	G	H3
Label	1	1	2	2	3	3	3	3	3	3	3	3
Dose	1	1 (bile exp.)	1	1	1	1	1	100	100	15 x 1	15 x 1	1 (bile exp.)
Sex	male	male	male	male	male	male	female	male	female	male	female	male
[h]	48	30	48	48	72	48	48	48	48	48	48	24
HEC 5725	3.2	8.3	0.5	1.0	6.3	1.7	2.5	53.8	43.0	7.1	7.5	7.6
1,2,3,4**	40.3	41.2	34.4	26.9	16.9	36.9	27.5	12.9	24.6	29.1	35.0	40.8
2,3,4	–	–	20.4	23.3	29.9	22.1	24.1	14.6	13.0	17.2	14.8	20.5
3,4	–	–	–	–	10.7	9.7	7.9	3.9	3.8	8.1	2.2	10.6
3	–	–	–	–	6.2	3.7	3.8	4.7	1.2	3.9	1.0	2.0
1,2**	9.8	5.3	5.7	6.1	–	–	–	–	–	–	–	–
Sum A	53.4	54.8	61.1	57.3	69.9	74.2	65.7	89.9	85.6	65.4	60.5	81.2
Sum B	19.8	28.3	22.0	23.6	19.7	19.9	18.6	8.3	8.7	18.0	13.5	20.2
Polar peak*	9.9	5.9	–	–	–	–	–	–	–	–	–	–
Sum C	83.1	89.1	83.1	80.9	90.0	94.2	84.5	98.6	94.5	83.8	74.0	101.8

* characterised by HPLC elution behaviour; contained at least 7 metabolites each at < 5 % of the total administered dose

** including 1 or/and 2 diene metabolites, each < 2 % of the dose

Sum A = Sum of parent compound and identified metabolites
Sum B = Sum of metabolites characterised by HPLC elution behaviour
Sum C = Sum of identified and characterised metabolites

Over all studies, the results obtained for the 3 different labels of fluoxastrobin are in good accordance with each other. No metabolite was detected unique for the ring 2-radiolabelled fluoxastrobin.

3.2 Metabolism in farm animals

The nature of the residues in the edible organs and tissues as well as in the milk and eggs of farm animals was investigated with [methoxyiminotolyl- and chlorophenyl-^{14}C]-labelled fluoxastrobin (Koester and Weber, 2001a, and Koester and Weber, 2001b, for the lactating goat; Klempner and Weber, 2001, and Klempner and Weber, 2002, for the laying hen). The goat serves as a model for ruminants, i.e. cattle while hens represent poultry. The results of these studies form the basis for the definition of the relevant residue in animal matrices.

3.2.1 Lactating goat

Methodology:

The metabolism and biokinetic behaviour of fluoxastrobin in lactating goats was investigated in two studies, in which either [chlorophenyl-UL-^{14}C]fluoxastrobin (ring 1-label) or [methoxyimino-tolyl-UL-^{14}C]fluoxastrobin (ring 3-label) was used. In each of the two studies on goats, one test animal received a dose of 10 mg of fluoxastrobin per kg body weight (bw) on three consecutive days. The compound was administered orally in a 0.5 % tragacanth suspension.
Based on the weight and feed consumption of the animals, this corresponded to a dose rate of 265 ppm (ring 1-label) or 180 ppm (ring 3-label) in the feed commodity. Compared to that 1× rate, the dosage of the metabolism studies is exaggerated by a factor of either 44 (ring 1-label) or 30 (ring 3-label).
The goats were sacrificed 5 hours after the last dosing (53 hours after the first administration), i.e. at a time when high concentrations of radioactivity are to be expected in milk, tissues and organs. The concentration vs. time course of total radioactivity in plasma was determined after the first administration in order to obtain information on the biokinetic behaviour.
Milk and edible organs and tissues were extracted by conventional methods and the nature of the residue was determined by analytical methods (radio-HPLC, LC-MS/MS).

Findings:

Excretion and residual radioactivity in the edible organs and tissues and in milk

Irrespective of the label, excretion of the fluoxastrobin-related residue was high. Until sacrifice, the excretion amounted to about 56-63 % of the total administered radioactivity. A portion of 11.7-17.5 % was excreted with the urine, and 44.1-45.1 % with the faeces. A very low amount (0.06-0.1 % of the dose) was secreted with the milk.
The residues, which remained in the edible organs and tissues of the sacrificed goats were calculated or estimated to be about 1.3-1.7 % of the dose. Based on these values, the overall recovery amounted to about 58-64 %. Since the goats were sacrificed just 5 hours after the last administration, the amounts not accounted for (about 40 %) were assumed to be present in the contents of the respective gastrointestinal tracts.

At sacrifice, the highest equivalent concentrations were measured in liver and kidney. This is in accordance with the liver being the primary site of degradation and kidney responsible for the excretion.

Identification and quantification of metabolites

In analogy to the plant and rat studies and due to the very high number of metabolites, which had been detected in the different goat samples (44 in total), the various metabolites were grouped by the rings or fragments of rings (see above).

The rate of identification amounted to either 58-92 % (ring 1-label) or 48-64 % of the TRR (ring 3-label). Furthermore 81-96 % (ring 1-label) or 73-93 % (ring 3-label) of the TRR were identified and/or characterised.

Fluoxastrobin was found in all sample materials. In fat, parent compound amounted to 12.0 % (ring 3-label) and 44.4 % (ring 1-label). The portion of parent compound in all other samples ranged from 0.3-7.3 % of the TRR.

Table 11: Distribution of fluoxastrobin and metabolites in consumable products of lactating goats

Radiolabel	ring 1-label					ring 3-label				
Sample matrix	ev.milk+	muscle	fat	liver	kidney	ev.milk+	muscle	fat	liver	kidney
TRR (mg/kg)	0.33	0.49	0.37	18.23	3.95	0.21	0.25	0.58	8.30	2.63
	Values expressed as percent of theTRR:									
HEC 5725	1.5	6.6	44.4	6.8	3.8	1.6	4.7	12.0	0.4	0.3
1,2,3,4	1.8	1.9	12.9	21.6	6.5	6.8	4.5	6.5	5.0	2.2
1,2,3,4 and 1,2,3 diene	13.0	15.0	4.1	6.3	5.8	7.4	10.8	3.1	4.0	5.7
2,3,4	–	–	–	–	–	3.1	4.7	–	4.0	8.3
1,2	14.6	52.9	29.0	14.2	33.8	–	–	–	–	–
1,2 diene	21.0	3.9	–	2.9	4.8	–	–	–	–	–
3,4	–	–	–	–	–	16.2	20.3	13.9	35.6	14.0
1	9.7	2.1	–	6.2	5.6	–	–	–	–	–
3	–	–	–	–	–	25.3	5.4	12.5	15.3	23.9
Sum A	55.9	80.6	73.4	52.3	40.2	52.8	44.7	47.9	51.6	49.7
Sum B	5.8	1.9	18.6	6.2	20.1	7.6	5.7	–	12.7	4.6
Polar peak*	9.5	2.5	–	8.1	17.0	–	–	–	–	–
Sum C	88.8	87.6	95.6	81.3	85.9	73.3	74.3	80.3	93.2	95.4
Not analysed**	7.5	0.5	2.2	2.0	0.7	11.8	4.0	18.0	–	3.1
Solids	3.8	12.0	2.2	16.8	13.5	15.0	21.7	1.7	6.8	11.6

\+ composite evening milk sample
* characterised by HPLC elution behaviour, containing up to 20 substance peaks depending on ring 1-label or ring 3-label
** sum of fractions obtained during the sample clean-up

Sum A = Sum of parent compound and identified metabolites
Sum B = Sum of metabolites characterised by HPLC elution behaviour
Sum C = Sum of identified and characterised metabolites

Major metabolites were the 3-ring metabolites (HEC 5725-2-cyanophenol, 2.6-9.0 % and its sulfate conjugate, 7.1-22.7 % of the TRR) and 1,2-ring metabolites (HEC 5725-phenoxy-hydroxypyrimidine, 8.3-52.9 % and its hydroxy derivatives, 2-11 % of the TRR). Additionally, HEC 5725-hydroxyphenyl (different isomers) was detected in fat and liver (11.4-13 % of the TRR) as well as a highly polar peak region eluting in the void volume of the standard HPLC. All other metabolites each accounted for less than 10 % of the TRR in any sample material. Detailed information is given in Table 11 and in Figure 3.

3.2.2 Laying hen

Methodology:

Either ring 1- or ring 3-radiolabelled HEC 5725 (isomer ratio 97 % E : 3 % Z) was administered orally on three consecutive days to six laying hens at a dose rate of 10 mg/kg body weight/day. Based on the weight of the animals and their feed consumption, this corresponded to a dose rate of 187 (ring 1-label) and 198 (ring 3-label) mg/kg (ppm) in the feed commodity. Compared to that 1× rate, the dosage of the metabolism studies is exaggerated by a factor of either 468 or 495.
The hens were sacrificed 5 hours after the last dose, at a time of relatively high radioactivity concentrations in the edible organs and tissues in order to provide sufficiently high residues for the identification of metabolites.
The eggs and the edible tissues were extracted and the nature of the residue was determined by analytical methods (radio-HPLC, LC-MS/MS). The TRR and metabolite levels are listed in Table 12.

Findings:

Excretion and residual radioactivity in the edible organs and tissues and in eggs

Irrespective of the label, excretion of the fluoxastrobin-related residues was high. Until sacrifice, the excretion amounted to about 72 % of the total administered radioactivity. Only a very low amount of 0.1 % of the total dose was determined in the eggs. Also, the residues in the edible tissues and organs were about only 2 % of the total dose. Consequently, the total radioactive residue (TRR) concentrations in the eggs, muscle, and fat were very low in relation to the dose. As primary organ for metabolism, the concentration in the liver was higher.

Identification and quantification of metabolites

The rate of identification amounted to either 63-80 % (ring 1-label) or 42-69 % of the TRR (ring 3-label). In total 78-84 % (ring 1-label) and 65-91 % (ring 3-label) of the TRR were identified and/or characterised.
The unchanged parent compound was found in all sample materials with the highest amounts being detected in fat. The portion of parent compound in these samples except fat ranged from 0.9-19.1 % of the TRR. The corresponding values for fat were 45.4 % (ring 3-label) and 47.7 % (ring 1-label).
In total 30 metabolites were identified. HEC 5725-phenoxy-hydroxypyrimidine was the major metabolite in all matrices ranging from 21-35 % of the TRR. In addition, HEC 5725-2-chlorophenol was found in significant amounts from 4 up to 23 % as well as HEC 5725-salicylic acid from 0.2 up to 12.2 % of the TRR.

Mainly in liver, various mono-, di- and tri-hydroxy 1,2,3,4-ring metabolites and their conjugates with sulfate and glucuronic acid were identified, each of them amounting to < 8 % of the TRR. A polar peak was detected additionally in all other sample materials of the ring 1-label (at about 6 % of the TRR), except for fat.

Beside these compounds, no other prominent metabolite was detected accounting for more than 10 % of the TRR in any sample material.

In analogy to the plant, rat and goat studies (see above), the numerous metabolites of fluoxastrobin were grouped by the rings or fragments of rings.

Detailed information is given in Table 12.

When residue concentrations are considered in the consumable products of lactating goats and hens, it should be kept in mind that both species were dosed 3 times in 24 hour intervals at a highly exaggerated rate (see above). Moreover, the animals were sacrificed 5 hours after the third dosing, at a time when a maximum concentration level was expected in organs and tissues in order to facilitate optimal metabolite identification.

Table 12: Distribution of fluoxastrobin and metabolites in consumable products of laying hens

Radiolabel	ring 1-label				ring 3-label			
Sample matrix	eggs	muscle	fat	liver	eggs	muscle	fat	liver
TRR (mg/kg)	0.12	0.38	0.68	8.05	0.32	0.53	0.9	9.47
	Values expressed as percent of theTRR:							
HEC 5725	10.5	19.1	47.7	0.9	14.5	12.9	45.4	2.6
1,2,3,4	5.8	2.7	5.7	18.0	5.4	4.5	9.3	32.5
1,2,3	2.4	1.6	1.9	4.5	6.1	3.6	12.3	3.7
1,2	25.7	36.2	21.2	28.1	–	–	–	–
3,4	–	–	–	–	1.6	2.4	1.0	4.1
1	26.6	12.0	3.5	11.6	–	–	–	–
3	–	–	–	–	15.6	18.2	0.9	16.4
Sum A	71.1	71.6	80.0	63.1	43.1	41.7	68.9	59.3
Sum B	2.3	1.1	3.9	9.4	22.1	34.3	12.8	31.7
Polar peak *	5.9	5.5	–	5.8	–	–	–	–
Sum C	79.3	78.2	83.9	78.3	65.2	76.0	81.7	91.0
Not analysed **	15.5	8.2	12.0	10.6	18.5	16.7	9.3	8.9
Sum of precipitates ***	–	–	–	–	12.4	6.1	–	–
Solids	5.2	13.6	4.1	11.1	3.9	1.1	9.1	0.0

* characterised by HPLC elution behaviour, containing up to 35 metabolites (each < 4 % of TRR) depending on ring 1- or ring 3-label

** sum of fractions obtained during the sample clean-up

*** precipitates during sample clean-up

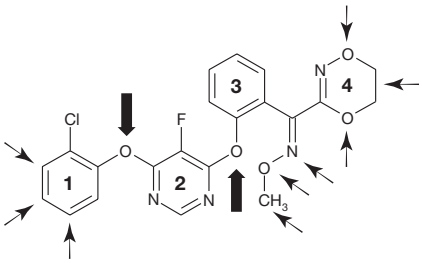
Sum A = Sum of parent compound and identified metabolites
Sum B = Sum of metabolites characterised by HPLC elution behaviour
Sum C = Sum of identified and characterised metabolites

4 Conclusion

The metabolic pathways in plants, rats and farm animals were well comparable. The following main metabolic reactions were found:

- hydroxylation of the chlorophenyl ring to monohydroxy- or dihydroxy-compounds including methoxylated metabolites,
- bis hydroxylation and reduction of the chlorophenyl ring to dihydroxy diene isomers,
- hydroxylation of the dioxazine ring,
- oxidative ring opening and further degradation of the dioxazine ring to the amide, followed by degradation to HEC 5725-2-cyanophenol and salicylic acid,
- cleavage of the ether group in the pyrimidine moiety to HEC 5725-2-chlorophenol and HEC 5725-des-chlorophenyl,
- cleavage of the ether group in the pyrimidine moiety to HEC 5725-phenoxy-hydroxy-pyrimidine and HEC 5725-des-pyrimidine including formation of amino-derivatives,
- oxidative demethylation of the oximether group and cleavage of the oximether to the ketone or alcohol,
- bis hydroxylation and reduction of the chlorophenyl ring of HEC 5725-phenoxy-hydroxypyrimidine to dihydroxy diene isomers and
- conjugation of hydroxy groups to mainly glucuronic acid-, methoxy glucuronic acid-, and sulfate-conjugates in animals,
- conjugation of hydroxy and thiol groups to glucosyl-, glucosyl-malonyl, glucosyl-sulfate-, and malonyl-conjugates in plants and
- isomerisation of the methoxyimino group with formation of the Z-isomers of fluoxastrobin and of respective metabolites in plants.

The following figure shows schematically the positions of the fluoxastrobin molecule, which are involved in metabolic reactions. An interesting finding was that the ring-systems 2 and 3 were not attacked by degradation reactions.



An overview of the biotransformation pathways of fluoxastrobin in plants and animals is given in Figure 3. Due to the high number of metabolites, the metabolic pathway is shown in two parts. The structures were limited to aglycons and many of the hydroxylated structures were also present as conjugates.

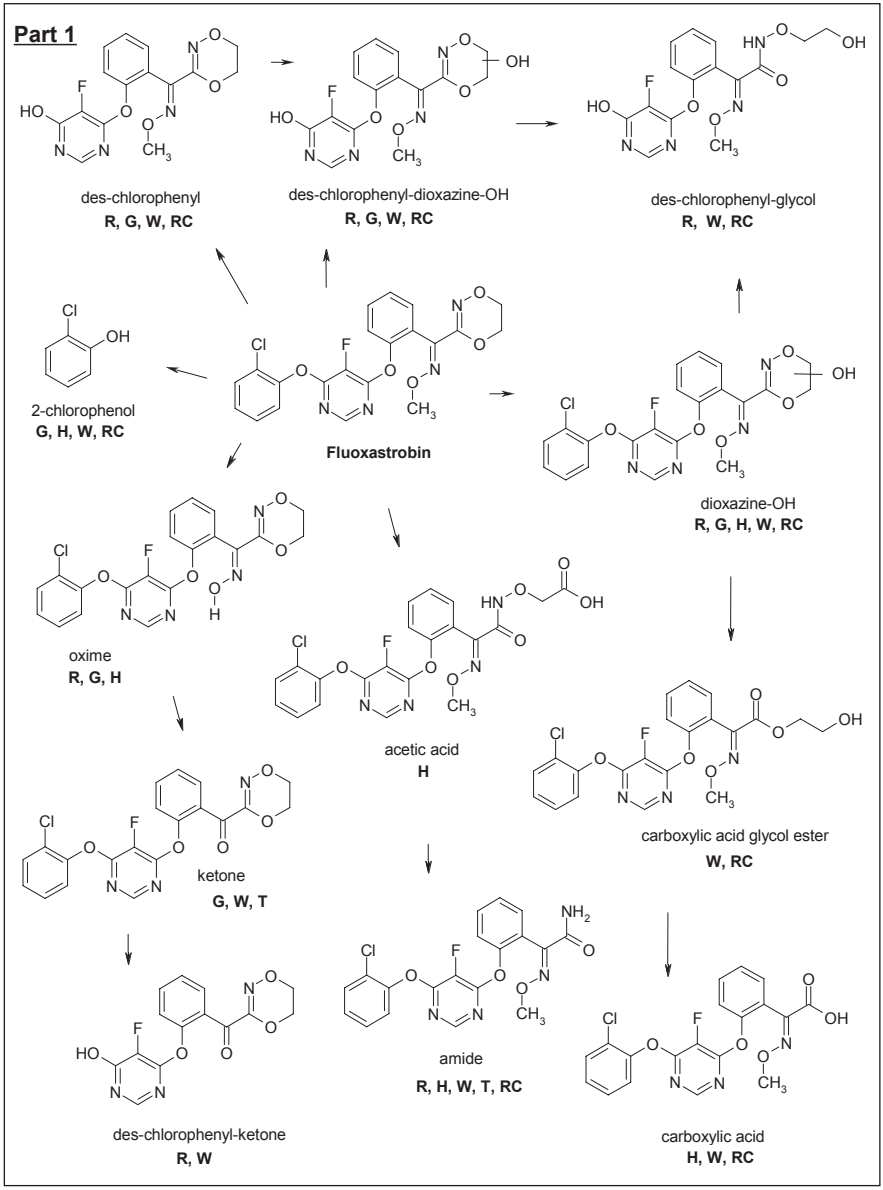


Fig. 3: Proposed metabolic pathway of fluoxastrobin in plants and animals
(R = rat; G = goat; H = hen; W = wheat; T = tomato; RC = rotational crops)

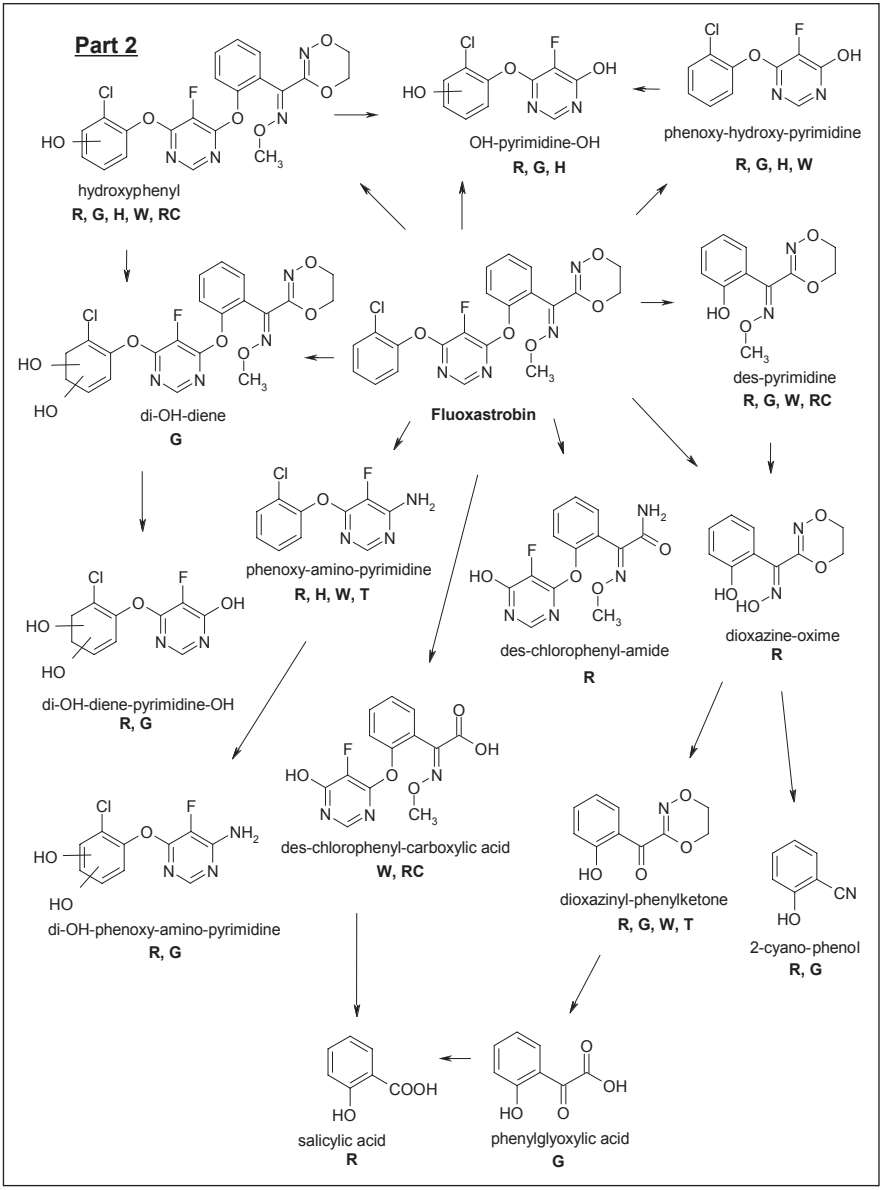


Fig. 3 continued: Proposed metabolic pathway of fluoxastrobin in plants and animals
(R = rat; G = goat; H = hen; W = wheat; T = tomato; RC = rotational crops)

5 Summary

Behaviour of fluoxastrobin (HEC 5725) in plants and animals

The metabolic pathways of fluoxastrobin in spring wheat, tomatoes and confined rotational crops were similar to those described for farm animals and the rat. Unchanged parent compound was the major constituent of the residue in crops including rotational crops. In spring wheat, a high number of metabolites was identified or characterised. Only a small number of metabolites was present in tomatoes. The identification and characterisation rate in plants was high and the nature of the residue was well understood.

After oral administration to the rat, fluoxastrobin showed a high absorption, a rapid distribution within the body and almost complete excretion mainly via bile and faeces. No organ or tissue contained appreciable radioactivity within a testing period of up to 48 hours except in the liver being the primary site for metabolism and in the kidney which is responsible for excretion. Similarly, the rapid excretion in the lactating goat and laying hen, serving as models for farm animals, ended in rather low residue concentrations in the edible organs and tissues as well as in milk and eggs. The degradation in the farm animals followed the same route as in the rat. Fluoxastrobin was detected in all sample materials and was the major component in the fatty tissues. Overall, the major metabolic reactions were hydroxylation, oxidation, hydrolysis and conjugation at different sites of the molecule. Based on the results of metabolism investigations, toxicological data and risk assessments, any risk to the consumer due to fluoxastrobin residues in animal and plant products can be ruled out.

Zusammenfassung

Untersuchungen zum Verhalten von Fluoxastrobin (HEC 5725) in Pflanzen und Tieren

Der Metabolismus von Fluoxastrobin in Sommerweizen, Tomaten und Nachbaukulturen war dem in landwirtschaftlichen Nutztieren und der Ratte sehr ähnlich. Der unveränderte Wirkstoff war der Hauptbestandteil des Rückstands in Pflanzen und nachgebauten Kulturen. Eine große Anzahl von Metaboliten wurde in Sommerweizen identifiziert oder charakterisiert. In Tomaten wurden nur wenige Metaboliten gebildet. Die Identifizierungs- und Charakterisierungsrate in Pflanzen war hoch und die Natur des Rückstands wurde umfassend aufgeklärt.

Fluoxastrobin wurde nach oraler Gabe in der Ratte sehr schnell aufgenommen, rasch im Tierkörper verteilt und schnell und fast vollständig überwiegend über die Galle und mit den Fäzes ausgeschieden. Innerhalb der Testperiode (48 Stunden nach Applikation) ergaben sich keine nennenswerten Rückstände in den Organen und Geweben der Ratte mit Ausnahme von Leber und Niere, die die wichtigsten Organe für Metabolismus und Ausscheidung sind. Wegen der schnellen Ausscheidung, die ebenfalls in den landwirtschaftlichen Nutztieren festgestellt wurde, waren die messbaren Rückstände in den essbaren Organen und Geweben sowie in der Milch und den Eiern sehr gering. Alle identifizierten Metaboliten waren durch die Rattenstudie abgedeckt. Fluoxastrobin wurde in allen Proben nachgewiesen und war in den Fettgeweben der Hauptrückstand. Die Hauptabbaureaktionen waren Hydroxylierung, Oxidation, Hydrolyse und Konjugation an verschiedenen Stellen des Moleküls. Auf Grund der vorgestellten

Ergebnisse, die zusammen mit toxikologischen Daten in Risikobetrachtungen verwendet werden, kann jegliche Gefahr für den Konsumenten durch pflanzliche und tierische Fluoxastrobin-Rückstände ausgeschlossen werden.

Résumé

Le comportement de la Fluoxastrobine (HEC 5725) dans les végétaux et les animaux

Le métabolisme de la fluoxastrobine dans du blé de printemps, des tomates et des cultures suivantes dans la rotation étaient similaires à celui décrit pour les animaux d'élevage et le rat. La matière active initiale inchangée était le composant principal du résidu retrouvé dans les plantes incluant les cultures suivantes dans la rotation. Un grand nombre de métabolites a été identifié ou caractérisé dans le blé de printemps, tandis que les tomates ne contenaient que peu de métabolites. Le taux d'identification et de caractérisation dans les plantes était élevé, et la nature du résidu bien établie.
Après administration orale chez le rat, la fluoxastrobine a montré une absorption très rapide, une prompte distribution dans l'organisme et une excrétion presque complète – surtout par voie biliaire et fécale. Pendant la période de test allant jusqu'à 48 h après application, aucune radioactivité appréciable n'a été observée ni dans les organes ni dans les tissus, à l'exception du foie – le site métabolique primaire – et du rein – le site de l'excrétion. Étant donné l'excrétion d'une rapidité similaire observée chez les animaux d'élevage, les résidus trouvés dans les organes et les tissus ainsi que dans le lait et les œufs étaient très faibles. Tous les métabolites identifiés ont été pris en compte dans l'étude chez le rat. La fluoxastrobine a été détectée dans tous les échantillons et elle était le composant principal dans les tissus adipeux. Les réactions métaboliques principales étaient l'hydroxylation, l'oxydation, l'hydrolyse et la conjugaison aux différents sites de la molécule. Sur la base des données des études de métabolisme, des données toxicologiques et des analyses de risques, le consommateur n'encourt pas de risque posé par des résidus de fluoxastrobine dans des produits d'origine animale ou végétale.

Resumen

Investigaciones sobre el comportamiento de Fluoxastrobin (HEC 5725) en plantas y animales

El metabolismo de fluoxastrobin en trigo de verano, tomates y cultivos de rotación fué muy similar al de los animales pecuarios y de la rata. El ingrediente activo sin modificar fué el principal componente del residuo en plantas y en los cultivos de rotación. Gran cantidad de metabolitos se identificó o caracterizó en trigo de verano. En tomates se formaron muy pocos metabolitos. La prorata de identificación y caracterización en plantas fué alta y la naturaleza del residuo pudo ser aclarada detalladamente.
Fluoxastrobin fué asimilado muy rápidamente después de su administración oral a la rata, con rápida distribución en el cuerpo del animal y rápida y casi completa eliminación, primordialmente vía biliar por las heces. Durante el período de evaluación (48 horas después de aplicación) no se dieron residuos mencionables en los órganos y tejidos de la rata con excepción del hígado y riñón, que son los principales órganos para metabolismo y excreción. Por la rápida excreción, obser-

vada también en los animales pecuarios, los residuos en los órganos y tejidos como también en la leche y huevos fueron muy reducidos. Todos los metabolitos identificados estaban cubiertos por el estudio en ratas. Fluoxastrobin se encontró en todas las muestras y fué el residuo principal en los tejidos adiposos. Las principales reacciones de degradación fueron hidroxilación, oxidación, hidrólisis y conjugación en diferentes partes de la molécula. En base a los resultados presentados, conjuntamente utilizados con los datos toxicológicos en las evaluaciones de riesgo, se puede excluír todo riesgo eventual por residuos vegetales y animales para el consumidor.

Резюме

Исследование поведения флуоксастробина (HEC 5725) в растениях и животных

Метаболизм флуоксастробина в яровой пшенице, помидорах и последующих культурах был очень похож на метаболизм в сельскохозяйственном пользовательном скоте и крысе. Неизмененное биологически активное вещество составляло основной компонент остатков в растениях и последующих культурах. Большое количество метаболитов идентифицировано или характеризовано в яровой пшенице. В помидорах образовалось только небольшое число метаболитов. Степень идентификации и характеристики в растениях была высокой, природа остатка была полностью выявлена.

При оральном введении флуоксастробин очень быстро поглощался крысами, быстро распространялся по всему организму животного и почти полностью выводился через желчный пузырь и с испражнениями. В течение времени испытания (первые 48 часов после аппликации) заметных остатков в органах и тканях крысы не наблюдалось, за исключением печени и почек, которые являются важнейшими органами метаболизма и выведения. Вследствие быстрого выведения, которое наблюдалось также у сельскохозяйственного пользовательного скота, остатки в органах и тканях, а также в молоке и яйцах были очень незначительными. Все идентифицированные метаболиты были определены в рамках исследования на крысах.

Флуоксастробин был обнаружен во всех пробах, и в жировых тканях он был главным остатком. Основными реакциями разложения были гидроксилирование, окисление, гидролиз и конъюгация в различных местах молекулы. На основе представленных данных, применяемых в сочетании с токсикологическими данными в анализах риска, можно исключить любую опасность для потребителей в связи с остатками флуоксастробина в растительном и животном материалах.

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