CLH Report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Penconazole**

EC Number: **266-275-6**

CAS Number: **66246-88-6**

Submitted by: **Germany**

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TABLES

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Penconazole

EC Number: 266-275-6

CAS number: 66246-88-6

Registration number (s): -

Purity: min. 950 g/kg

Impurities: There are a number of impurities claimed as confidential by the producer

Proposed classification based on Directive 67/548/EEC criteria:

Health hazards: Xn; R22

Environment: N; R50-53

Proposed classification based on GHS criteria:

Health hazards:

Acute Tox. 4 H302

Environment:

Aquatic acute 1 H400

Aquatic chronic 1 H410

Proposed labelling:

Directive 67/548/EEC:

Symbol: Xn, N

Risk phrases: R22-R50/53

Safety phrases: S60-61

Regulation EC1272/2008 (GHS criteria):

Pictogram: GHS07, GHS09

Signal word: Warning

Hazard statement codes: H302, H410

Proposed specific concentration limits (if any):

Environment

Specific concentration limits based on Directive 67/548/EEC:

Concentration	Classification
$C \geq 25\%$	N; R50-53
$2.5\% \leq C < 25\%$	N; R51-53
$0.25\% \leq C < 2.5\%$	R52-53

Where C is the concentration of penconazole in the preparation.

M-factor based on Regulation EC 1272/2008

The M-factor is determined by using the reported ErC50 value of 0.22 mg/L obtained for the aquatic plant *Lemna gibba* in a 14 d static study. Consequently, an M-factor of 1 is assigned.

Proposed notes (if any):

None

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name: 1-[2-(2,4-dichlorophenyl)pentyl]-1H-1,2,4-triazole

EC Name: 266-275-6

CAS Number: 66246-88-6

IUPAC Name: 1-[2-(2,4-dichloro-phenyl)pentyl]-1H-1,2,4-triazole

1.2 Composition of the substance

There are a number of impurities claimed as confidential by the producer.

Substance is a racemate i.e. 1:1 mixture of R and S isomer.

Chemical Name: 1-[2-(2,4-dichlorophenyl)pentyl]-1H-1,2,4-triazole

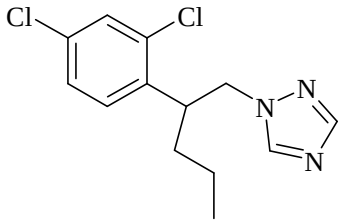
EC Number: 266-275-6

CAS Number: 66246-88-6

IUPAC Name: 1-[2-(2,4-dichloro-phenyl)-pentyl]-1H-1,2,4-triazole

Molecular Formula: $C_{13}H_{15}Cl_2N_3$

Structural Formula:



Molecular Weight: 284.2 g/mol

Typical concentration (% w/w): confidential data

Concentration range (% w/w): > 950 g/kg

1.3 Physico-chemical properties

Table 1.3-1: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	white powder (purity 99.5 %) off-white powder with lumps (purity 96.1 %)	Draft Assessment Report Monograph EFSA conclusions
VII, 7.2	Melting/freezing point	3.2	60.3 – 61.0 °C (purity 99.5 %)	
VII, 7.3	Boiling point	3.3	> 360 °C at 101.3 kPa (calculated)	
VII, 7.4	Relative density	3.4 density	1.28 g/cm^3 (purity 99.5 %)	
VII, 7.5	Vapour pressure	3.6	3.66x10^{-4} Pa (25 °C), extrapolated from measurements at 36.6 and 58.3 °C (purity 99.5 %)	
VII, 7.6	Surface tension	3.10	59.7 to 62.8 mN/m (20 °C, purity 96.1 %)	
VII, 7.7	Water solubility	3.8	73 mg/L (at 20 °C, pH 6.7, purity 99.5 %)	
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	3.72 (25 °C, pH 5.65)	
VII, 7.9	Flash point	3.11	not relevant	
VII, 7.10	Flammability	3.13	not highly flammable (purity 96.1 %)	
VII, 7.11	Explosive properties	3.14	not explosive (purity 96.1 %)	
VII, 7.12	Self-ignition temperature		no self ignition observed up to melting temperature (purity 96.1 %)	
VII, 7.13	Oxidising properties	3.15	no oxidising properties (purity 96.1 %)	
VII, 7.14	Granulometry	3.5	not determined	
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	not determined	
XI, 7.16	Dissociation constant	3.21	pKa = 1.51	
XI, 7.17,	Viscosity	3.22	not determined	
	Auto flammability	3.12	no self ignition observed up to melting temperature (purity 96.1 %)	
	Reactivity towards container material	3.18	not determined	
	Thermal stability	3.19	no thermal effect between room temperature and 150	

			°C (purity 96.1 %)	

2 MANUFACTURE AND USES

2.1 Manufacture

Confidential information.

2.2 Identified uses

Penconazole is an agricultural fungicide which is used by foliar application to control a wide range of diseases in fruits and vegetables.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

None

3.2 Self classification(s)

Not relevant for this dossier.

4 ENVIRONMENTAL FATE PROPERTIES

The environmental fate properties assessment for penconazole is based on the Draft Assessment Report and Proposed Decision of Germany prepared in the context of the possible inclusion of penconazole in Annex I of Council Directive 91/414/EEC (DAR June 2007 + Final addendum July 2008, RMS Germany).

4.1 Degradation

4.1.1 Stability

Hydrolysis

- van der Gaauw, A., (2002), Report No.: 841774, Docs ID: WAS 2004-399

Under sterile aqueous conditions at 50 °C penconazole (CGA 71818) was found to be hydrologically stable over 7 days at pH 4, 5, 7 and 9, respectively. The study was performed according to OECD 111 (1981) with ^{14}C-phenyl labelled penconazole (specific radioactivity: 2.3 MBq/mg; radiochemical purity: 98.2 %) dissolved in sterile buffers at a concentration of 1.8 to 1.9 mg as/L. Mean recoveries of total radioactivity during the 7-day incubation period were 96.1 ± 3.2 %, 95.5 ± 3.2 %, 95.8 ± 3.5 %, and 94.5 ± 3.3 % AR for pH 4, 5, 7 and 9, respectively. The test substance penconazole was stable under all test conditions representing ≥ 98 % of radioactivity at each pH and sampling interval.

- Spare, W.C. (1987); Report No. 1284, Docs ID: WAS 2004-400

Under sterile aqueous conditions at 25 °C penconazole (CGA 71818) was found to be hydrologically stable for up to 30 days at pH 5, 7 and 9, respectively. The study was performed according to EPA Pesticide Assessment Guidelines, Subdivision N, Environmental Fate (October 1982), Series 161-1 with ^{14}C-Triazole labelled penconazole (specific radioactivity: 0.77 MBq/mg, radiochemical purity: 98.3 %) dissolved in sterile buffers at a concentration of 10 mg as/L. Mean recoveries of total radioactivity during the 30-day incubation period were 102.5 ± 7.3 %, 98.2 ± 4.4 %, and 91.8 ± 4.4 % of the initial radioactivity (AR) for pH 5, 7 and 9, respectively. For the three pH solutions penconazole accounted for 95.6, 98.8 and 98.0 % of the applied dose at day 30.

Photolysis in water

Data on the direct aqueous photolysis of penconazole or its degradates is not required since the molar absorption coefficient ε is < 10 L mol^{-1} cm^{-1}. No data available in DAR! Test provided for ZA 5519

Photolysis in soil

- Mamouni, A., 2003, Report No.: 826694, Doc ID: BOD2004-952

The photolytic degradation of ^{14}C-phenyl labelled penconazole (specific activity: 2.3 MBq/mg, radiochemical purity 100 %) under artificial sunlight was studied following application to a silt loam soil. The treatment of soil resulted in an approximate soil concentration of 14.35 mg as/kg soil

(equivalent to a field rate of 181 g as/ha). Irradiation was performed with a Heraeus “Suntest” unit (Hanau/D) with a xenon arc lamp equipped with an UV filter to cut off light of less than 290 nm (mean light intensity for 300 -400 nm: 41.8 W/m^2). The soil temperature during the experiment was maintained at 21.2 to 21.8 °C and the irradiation regime was performed with a 12 hours light/12 hours dark cycle (irradiated samples) or in dark (non-irradiated samples) for 29 days. Half-lives were calculated by extrapolation using the corrected penconazole percentages and applying pseudo first-order reaction kinetics (non-linear curve fitting, one compartment model).

Under the experimental conditions, penconazole was slowly broken down by light with a half-life of 259 days corresponding to 282 days at latitude 50 °N. According to published data summer light at 50° N is equivalent to 95.3 % and 96.3 % of summer light at latitude 30 °N and 40 °N, respectively. This results in half-lives of penconazole of 269 and 271 at latitude 30 and 40 °N, respectively. Under dark conditions practically no degradation of penconazole was found.

- Spare, W.C., 1987, Report No.: 1282-A, Docs ID: BOD 2004-953

The photolytic degradation of ^{14}C-phenyl labelled penconazole (specific activity: 0.77 MBq/mg, radiochemical purity: 98.3 %) under natural light was studied following application to a clay loam soil for a period of 30 days. Natural sunlight intensity at the test facility (39°25´ N latitude and 77°24´ W longitude) was measured to range from 0.1 to 20 W/m^2 during the exposure period with the UVM and 0.0017 to 0.35 W/m^2 with the International Light Meter (ILI 700). The soil surface was treated with 0.1 mL of the application solution (= ca. 20 µg as) resulting in a dose of ca 10 mg as/kg, corresponding to a surface treatment rate of 25 g as/ha based on a soil film area of 78.5 cm^2. The treated soil samples were exposed to natural sunlight on the roof of the laboratory for 30 consecutive days. Air temperature varied between -1 °C and 29 °C during the test period.

The findings in the study indicate that direct photolytic degradation of penconazole under natural sunlight is very slow. For the sunlight exposed test systems a dissipation half-life of 148 days was calculated for penconazole using pseudo first-order reaction kinetics, whilst no dissipation occurred in the dark control test systems.

<u>Photo-oxidative degradation in air</u>

- Stamm, E., 1999, Report No.: 95A99002SM, DOC ID: LUF 2004-160

The half-life of penconazole in the atmosphere was calculated as being in the range of 1.32 to 1.99 days dependent upon the mean aerial OH concentration chosen for the calculation, 0.5 x 10^6 cm^{-3} averaged over a 24 hours or 1.5 x 10^6 cm^{-3} averaged over 12 hours, respectively. The calculations according to the Atkinson method were based on the AOP version 1.85 for the calculation with 0.5 x 10^6 cm^{-3} and AOP version 1.91 for the calculation with 1.5 x 10^6 cm^{-3}. It can be concluded that penconazole will be readily degraded in the air due to its fast reaction with photolytically generated hydroxyl radicals.

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

No data available.

4.1.2.2 Screening tests

Readily biodegradability

- Grade, R., 1999, Report No.: 993529, Doc ID: WAS 2000-305

The ready biodegradability of penconazole was determined according to the OECD Guideline No. 301B. The test was performed with penconazole technical grade (96.6 % purity; carbon content 54.94 % based on the empirical formula $C_{13}H_{15}C_{l2}N_3$) in a mineral medium inoculated with activated sludge collected from a sewage treatment plant (CH-4153 Reinach, Switzerland). The test system is described in Table 4.1-1. During incubation the evolved carbon dioxide was measured at 0, 3, 6, 8, 10, 13, 16, 20, 24, 28 and 29 days. The percentage of degraded test substance was calculated by comparing the quantities of inorganic carbon (CO_2) measured in the absorber flasks at the respective sampling intervals with the theoretical carbon content.

There was no biodegradation (0 % of the theoretical value) of penconazole within 29 days. The reference substance was degraded to 91 % within a 10-day time window. According to these findings, penconazole is classified as “not readily biodegradable” (cf. Annex VI of Directive 67/548/EEC).

Table 4.1-1: Test system for carbon dioxide evolution study

Source:	Sewage treatment plant, CH-4153 Reinach, Switzerland
Date of collection:	23.08.1999
pH of inoculum:	7.2 (after collection)
Concentration of inoculum:	25.3 mg sludge/L
Test substance concentration:	40.8 – 41.1 mg as/1.5 L, corresponding to 14.9 – 15.1 mg ThOC/L*
Test conditions:	2 L dark brown glass flasks; 20 ±2 °C
Reference substance:	Sodium benzoate, 15 mg DOC/L*

*ThOC = Theoretical Organic Carbon; DOC = Dissolved Organic Carbon

4.1.2.3 Simulation tests

Biodegradation in water/sediment systems

- Mamouni, A., 1998, Report No.: 616860, Doc ID: WAS 2000-306

The distribution, degradation and metabolism of ^{14}C-phenyl labelled penconazole (specific radioactivity: 2.12 MBq/mg, radiochemical purity: ≥ 99 %) in equilibrated water-sediment systems were investigated. The study was performed according to the guidelines BBA-Richtlinie Teil IV, 5-1 "Abbaubarkeit und Verbleib von Pflanzenschutzmitteln im Wasser/Sediment System" (1990), Commission Directive 95/36/EC (1995) and SETAC Europe, Part 8.2 (1995). The water-sediment systems from a river and from a pond consisted of natural water filtered through a 0.2 mm sieve, and the uppermost 5 to 10 cm of sediment sieved through a 2 mm mesh (characterisation of the systems see Table 4.1-2).

Table 4.1-2: Water/sediment characteristics of river and pond systems

System	**River**		**Pond**	
Source	**Rhine, Mumpf, Aargau/CH**		**Judenweiher, Rheinfelden, Aargau/CH**	
Date of sampling	11.06.1996		09.04.1996	
	start of the test	end of the test	start of the test	end of the test
Sediment characteristics:				
Sand (%)	47.1	n.d.	44.9	n.d.
Silt (%)	38.0	n.d.	31.8	n.d.
Clay (%)	14.9	n.d.	23.3	n.d.
pH (H_2O / $CaCl_2$)	7.3 / 6.9	n.d.	7.6 / 6.7	n.d.
Total nitrogen (g/kg sediment)	4.15	n.d.	2.43	n.d.
Total phosphorous (g/kg sediment)	0.947	n.d.	0.932	n.d.
Organic carbon (%)	2.10	n.d.	2.82	n.d.
CEC (mVal/100g)	112.0	n.d.	137.9	n.d.
Biomass (mg C/100g dry sediment)	132.3	71.56	79.64	73.21
Water characteristics				
pH	7.66	8.15	7.94	8.06
Oxygen content (mg/L)	8.5	6.6	14.7	6.7
TOC (mg C/L)	3.1	10.4	6.7	5.1
Total nitrogen (mg/L)	2.6	n.d.	1.7	n.d.
Hardness (°dH)	13	28	19	56
Redox potential (mV)	224	203	234	176

n.d. = not determined; TOC = total organic carbon

The incubation of the test systems was performed at 20° C in the dark over 365 days. However, additional samples were taken after 678 and 706 days for the river and pond system, respectively, to account for the course of the concentration of the metabolite CGA 179944.

The results of the aerobic incubation are summarised in

Table 4.1-3: Dissipation times of ^{14}C-phenyl labelled penconazole in aquatic systems

Substance	**Test system**	**Total system (days)**		**Water (days)**		**Sediment (days)**	
		DT_{50}	DT_{90}	DT_{50}	DT_{90}	DT_{50}	DT_{90}
Penconazole	River	505	> 678	2.2	7.4	505	> 678
	Pond	> 706	> 706	3.3	11.0	> 706	> 706

The results summarized in Table 1.3-1 indicate that penconazole is very rapidly adsorbed on to sediment and is relatively slowly degraded in that state. Due to the rapid adsorption to sediment, the degradation rate in the water phase cannot be determined, however, it is likely to be slow. For a compound so rapidly adsorbed to sediment the total system half-life is an approximate value to also represent the sediment degradation half-life. Therefore, for environmental assessment the longest value determined at 20 °C is recommended for use, i.e. 706 days.

CGA 179944 was the only major metabolite occurring at maximum amounts of 22 % in the river system and 6 % in the pond system. The half-life of CGA 179944 in the river system was estimated to be ~ 235 days. No calculation was possible for the dissipation of CGA 179944 from the pond system due to the low amounts formed. Small amounts (< 3 % of the applied dose) of four unknown metabolites were found in the water and sediment compartments of the aquatic systems.

Biodegradation in soil

Under laboratory conditions the rate of degradation of penconazole was examined in a number of experiments in various soil types and partly at different temperatures. The kinetic data of the studies are discussed in detail in the chapter B.8.1.2.1 of Addendum 1 (April 2008) to the EU draft assessment report of penconazole. The degradation rates of penconazole in aerobic laboratory soils have been determined in accordance with the latest guidance resulting from FOCUS Kinetics. Half-lives were determined on the base of the original data from the studies re-fitted using non-linear regression and single first order fit (SFO). To obtain the overall average half-life of penconazole in soil the half-lives were first averaged for individual soils and then the averaged overall. The resulting maximum is 173 days in aerobic normalized laboratory studies. In aerobic laboratory soil degradation studies the resulting overall geometric mean half-life of penconazole at 20 °C and pF2 is 117 days (SFO, range 55.3 – 207 days, n = 10) and the overall median half-life of 145 days. The results of the experiments are summarised in Table 4.1-4.

Table 4.1-4: Overview on degradation of penconazole in aerobic laboratory studies

Reference Report No. Doc ID	Location/ Soil type	Temp. (°C)	Moisture	pH	Application rate (mg/kg soil)	DT_{50} (days)	χ^2 Error %	Normalised DT_{50} (days)	DT_{50} for soil groups
Völkl (2002) 822778 BOD 2004-950	Weide, CH Silt loam	20	40% MWC	7.5	0.278	158	2.92	158	158
	Pappelacker, CH Sandy loam	20	40% MWC	7.4	0.278	55.3	4.06	55.3	55.3
Glänzel (1999) 98AG01 BOD 2000-556	Gartenacker, CH Loam	20	40% MWC	7.2	0.42	79.6	4.61	79.6	79.6
Knoch, 1993 246903 BOD 98-00096	Itingen III, CH Silt loam	10	60% FC	7.4	0.838	488	2.95	155	132
		20	60% FC	7.4	0.838	142	7.63	99.3	
		20	30% FC	7.4	0.838	480	3.44	207	
		20	60% FC	7.4	0.084	138	6.52	96.5	
Abildt (1989) 08/89 BOD 98-00486	Le Barges, CH Sandy loam/ loam	25	75% FC	7.0	0.97	155	9.69	188	173
Abildt (1989) 09/89 BOD 98-00485	Le Barges, CH Sandy loam/ loam	15	75% FC	7.0	0.97	289	4.81	159	
Keller, 1982 41/82 BOD 98-00095	Le Barges, CH Sandy loam	25	75% FC	7.3	1.0	134	2.53	163	163

Aerobic laboratory soil degradation studies and field soil dissipation trials demonstrated that penconazole is degraded under non-sterile incubation conditions to several metabolites and non-extractable residues and progressively but slowly mineralised to carbon dioxide. Most metabolites found in aerobic penconazole degradation studies were minor metabolites accounting for less than 5 % of the applied radioactivity (AR). Identification was not generally possible due to the low amounts formed and transient occurrence. Whereas in studies with labelled 1,2,4-triazole ring two metabolites exceeding 10 % AR were observed (CGA 179944: max. 18.9 % AR; CGA 71019: max. 38.6 % AR) no major metabolites were occured in the studies with labelled phenyl ring. In 6 studies with triazole labelled penconazole a negligible to very low mineralization (CO_2: 0.2 – 6 % AR after 84 – 120 d) was observed in combination with the formation of significant amounts of non-extractable residues (6 – 25% AR after 84-120 days). In 2 studies with phenyl labelled penconazole a moderate mineralization (CO_2: 15 – 19 % AR after 84 – 182 d) was observed in combination with the formation of significant amounts of non-extractable residues (13 – 15% AR after 84-182 days). Organic matter fractionation demonstrated that about two thirds of the non-extractable residues were associated with the humic and fulvic acid fractions, whilst one third was still bound to the insoluble humin fraction even after excessive extraction.

Field dissipation studies were undertaken at various sites on bare ground plots located in Germany and France. No significant effect of the location on the field dissipation rate was observed. In these trials SFO DT_{50} in the range from 67 to 115 days were observed. The kinetic data of the studies are discussed in detail in the chapter B.8.1.2.2 of Addendum 1 (April 2008) to the EU draft assessment report of penconazole. The results are summarised in Table 4.1-5:

Table 4.1-5: Overview of field soil dissipation times for penconazole

Reference Report No. Doc ID	**Location/ Soil type**	**pH**	**Depth (cm)**	**Application rate (g as/ha)**	**DT_{50} (days)**	**DT_{90} (days)**	**Method of calculation**
Offizorz, 1990 172800 BOD98-00511	Schornbusch, Germany loamy soil	7.5	0 - 20	1 x 500	67 [1)]	221	SFO
Offizorz, 1991 217427 BOD98-00515	Meissner-Vockerode, Germany loamy sand	7.2	0 - 20	1 x 500	84 [1)]	290	SFO
Offizorz, 1991 217438 BOD98-00517	Weeze-Wemb, Germany Sand	7.4	0 - 20	1 x 500	84 [1)]	279	SFO
Offizorz, 1991 217451 BOD98-00513	Plattling-See, Germany loamy silt	7.0	0 - 20	1 x 500	107 [2)]	355	1st
Tournayre, 1985 36-84 BOD98-00488	Codognan, France clay loam	7.3	0 - 20	1 x 200	(96) [2) 3)] 115 [4)] 22 [4) 5)]	(319) 380 320707	1 st SFO FOMC

[1)] Origin software (Microcal, version 5)
[2)] linear recression (MS Excel)
[3)] without day 240,
[4)] alphaP= 0.168, betaP=0.361, Pini= 0.159
[5)] considering the SFO DT_{50} of 115 d from Codognon, F

4.1.3 Summary and discussion of persistence

Biodegradation in water

Penconazole was found to be not readily biodegradable.

In water/sediment systems penconazole dissipated primarily by partitioning to the sediment with single first order DT_{50} of 1.9-3.4 days where it subsequently degraded (whole system pseudo first order DT_{50} 505 up to >706 days) forming the major metabolite CGA 179944 that was present in the

water phase (max. 17.3 % of AR after 365 days) and only accounted for a maximum of 4.8% of AR in the sediment.

Biodegradation in soil

In aerobic laboratory soil degradation studies the overall geometric mean DT_{50} value of penconazole is 117 days (SFO, 20 °C, pF2). In field dissipation studies DT_{50} values of penconazole were in the between 67 d – 115 days (SFO).

Based on the findings from the screening test on ready biodegradability, water/sediment simulation test and soil penconazole appears to be susceptible for primary degradation and not ultimate mineralisation. Considering the results of the test on ready biodegradability and levels of mineralisation in the simulation study, penconazole is considered not readily biodegradable (a degradation of >70% degradation within 28 days) for purposes of classification and labeling.

4.2 Environmental distribution

Not relevant for this dossier.

4.2.1 Adsorption/desorption

4.2.2 Volatilisation

4.2.3 Distribution modelling

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

Penconazole has a log Kow of 3.72 (pH 5.65, 25 ºC, destilled water).

Measured bioaccumulation data

For [^{14}C]-penconazole a maximum bioconcentration factor (BCF) of 320 L/kg ww on day 1 and a steady state BCF of 200 L/kg ww based on total radioactive residue and whole fish was derived from a study with bluegill sunfish (*Lepomis machrochirus*). The mean ^{14}C residue in the edible (muscle) tissue and in whole fish reached a mean maximum concentration of 20 and 14 mg/kg on day 1. The mean ^{14}C residue in the non-edible tissue reached a mean maximum concentration on day 7 of 16 mg/kg. Analysis of fish samples taken during the depuration phase, indicated 50 % of the accumulated ^{14}C residues was eliminated by day 3 of the depuration phase. By day 7 of the depuration phase 96, 97 and 97 % of the ^{14}C residues present in the edible tissue, viscera and whole body, respectively, on the last day of exposure, had been eliminated.

The studies are summarised in Table 4.3-1.

Table 4.3-1: Results of aquatic bioconcentration measurement

guideline/ test method	exposure	log Kow	Initial conc. [µg/L]	Steady state BCF [L/kg ww]	Kinetic BCF	Depuration time CT_{50} (d)	Depuration time CT_{95} (d)	Remarks	Reference Report No. Doc ID
EPA Guideline No. 165-4	28 d, flow - trough	3.72	44 (real) 54 (nom)	200	n.d.	3	7	Whole fish based on total radioactive residues	Surprenant D.C. (1988) BW-85-2-1729 WAT 96-50100

4.3.2 Terrestrial bioaccumulation

No data available.

4.3.3 Summary and discussion of bioaccumulation

Penconazole has a log Kow of 3.72. The experimentally derived steady state BCF of 200 (based on total radioactive residue for whole fish) is above the trigger of 100 (criterion for bioaccumulating potential conform Directive 67/548/EEC) but lower then 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008) for not readily biodegradable substances. Based on the results of the bioconcentration study, penconazole does significantly bioaccumulate.

4.4 Secondary poisoning

Not relevant for this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

Penconazole has been reviewed under Council Directive 91/414/EEC. For more detail on the studies described or mentioned below reference is made to the Draft Assessment Report, the final addendum to the DAR, and the EFSA conclusions.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Penconazole is extensively absorbed from the gastro-intestinal tract (> 80 % based on urinary and biliary excretion within 48 h) and widely distributed without bioaccumulation in body tissues. Liver, kidneys, adrenal glands and abdominal fat are the most highly exposed tissues. The systemic exposure (AUC) in male rats is about twice the exposure in females. Penconazole is extensively metabolised, showing quantitative differences between males and females in metabolic pathways but a similar range of metabolites. The identified biotransformation reactions include cleavage of the carbon-nitrogen bond leading to the formation of 1,2,4-triazole as one of the main metabolites (15 % of dose), oxidations and conjugations. Excretion was rapid and quantitative (> 95 % within 72 h). The urinary excretion is higher in females (70-85 % via urine, 15-30 % via faeces) than in males (45-60 % via urine, 40-50 % via faeces), and the biliary excretion is higher in males (55 % vs 40 % in females). This indicates a sex-specific difference in the production of polar metabolites in rats. Residues at higher level than in blood were found in liver, kidneys, adrenal glands and thyroid (Van Dijk A., 1988, Report No. RCC 075666; Hamboeck, H., 1980, Report No. 41/80; Hamboeck, H., 1982, Report No. 15/82; Hamboeck, H., 1984, Report No. 23/83; Hamboeck, H., 1985, Report No. 1/85; Hassler, S., 1999, Report No. 039AM01; Levan, L., 1987, Report No. HLA 6117-123; Hiles, R., 1987, Report No. HLA 6117-121; Hiles, R., 1987, Report No. HLA 6117-122).

Dermal application in vivo (6 h exposure) indicated dermal absorption of up to 6 % for a concentrated (1 mg/cm^2) and 32 % for a diluted (0.5 µg/cm^2) preparation in male rats (Hassler, S., 2000, report no. 039AM02). In vitro, rat and human skin (including stratum corneum) showed 15 % and 1 % dermal absorption with the concentrate, and 50 % and 8 % respectively, with the diluted formulation. (Hassler, S., 2000, report no. 039AM03) Taking into consideration the differences in penetration through rat and human skin in vitro and using the rat/human in vitro absorption ratios of 15.1 and 6.25, the absorption through human skin in vivo is estimated to be < 1 % for a concentrate and 5 % for the spray strength dilution, respectively.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

In the rat, the maximum non-lethal dose was 1000 mg/kg bw in males and 500 mg/kg bw in females. Lethality began to occur 2-3 hours after dosing. The LD_{50} for males was below 2000 mg/kg bw; 3 of 5 animals at this dose died. Clinical signs consisted of sedation, dyspnoea, curved or lateral/ventral body position, ruffled fur, and diarrhoea. They were observed from one hour after dosing and persisted for up to 9 days, Gross pathology did not show any particular findings in any organ or tissue at necropsy, neither in decedents nor in surviving animals. Similar clinical signs and toxicity following acute oral exposure to penconazole were also observed in the other species tested, with rabbits being similarly or more sensitive than rats.

Table 5.2-1: Summary of acute oral toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Remarks	Reference
OECD 401	Oral	Rat, Tif: RAI f (SPF) 5M+5F	500-1000-2000-4000	LD_{50} (M+F) 1486-3831 LD_{50} (M) < 2000	Vehicle: polyethylene glycol (PAG 400)	Bathe, R. (1980); report no 800553
OECD 401	Oral	Chinese hamster, 5M+5F	2000-4000-5000	LD_{50} (M+F) ≈ 5000 4000 < LD_{50} (F) < 5000	Vehicle: polyethylene glycol (PAG 400)	Bathe, R. (1980); report no 800555
OECD 401	Oral	Mouse, Tif:MAG (SPF) 5M+5F	1500-2000-3000-5000	LD_{50} (M+F) 2444	Vehicle: polyethylene glycol (PAG 400)	Sarasin G. (1980); report no 800552,
OECD 401	Oral	Rabbit, NZW 5M+5F	0-600-1000-2000	LD_{50} (M+F) 971	Vehicle: aqueous 2% carboxy-methylcellulose	Kobel W. (1981); report no 800554,

5.2.2 Acute toxicity: inhalation

Penconazole was of very low acute inhalation toxicity in rats. No deaths occurred. Symptoms included slight to moderate sedation (at the 4 h time point only), moderate to severe dyspnoea, curved body position and ruffled fur, which were observed in all animals at the end of the 4 h inhalation exposure and thereafter. In rats exposed to penconazole, symptoms were of a slightly more severe grade than in the vehicle control group and lasted 2 days longer. All rats had recovered completely on day 5 (control) and day 7 post-exposure (test group), respectively.

Table 5.2-2: Summary of acute inhalation toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/L)	Value LC_{50} (mg/L)	Remarks	Reference
OECD 403	Inhalative	Rat, Tif: RAI f (SPF) 5M+5F	0-4.05	LC_{50} > 4.05	Dust aerosol as a mixture with vehicle: aluminium oxide and Sipernat 50 S, 4-h, nose only; highest attainable concentration	Hartmann H. (1987); report no 871169,

5.2.3 Acute toxicity: dermal

Penconazole was of very low acute dermal toxicity in rats. No deaths occurred. Slight symptoms of toxicity were observed in all groups receiving penconazole, with an onset during the first hour after application and a duration of up to 7 days. Symptoms included dyspnoea, ruffled fur, and curved body position. Necropsy revealed no abnormal changes..

Table 5.2-3: Summary of acute dermal toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Remarks	Reference
OECD 402	Dermal	Rat, Tif:RAIf 5M+5F	0-2000-2500-3000	LD_{50} (M+F) >3000	Vehicle: not stated in report	Bathe, R. (1980); report no 800559,

5.2.4 Acute toxicity: other routes

No data are available.

5.2.5 Summary and discussion of acute toxicity

The LD_{50} for male rats was below 2000 mg/kg bw, the classification threshold for harmfulness. Female mortality data from the study were inconclusive lacking a clear dose response. Given the large confidence interval, the meaningfulness of a combined LD_{50} estimate can be questioned..The combined acute oral LD_{50} for male and female rabbits was calculated to be 971 mg/kg (limits of confidence: 645 - 1321 mg/kg). Based on the results of the acute oral LD_{50} test in rats and in rabbits, penconazole is considered 'harmful if swallowed'. No classification or labelling is required for acute dermal or inhalative toxicity.

Classification and Labelling for acute toxicity according to Directive 67/548/EEC:

Xn; R22 (Harmful if swallowed)

Classification and Labelling for acute toxicity according to GHS:

Acute Tox. 4; H302 (Harmful if swallowed)

5.3 Irritation

5.3.1 Skin

Penconazole was not irritating to rabbit skin when applied for 24 h as moistened powder at a dose of 83 mg/cm^2.

Table 5.3-1: Summary of skin irritation

Method/ Guideline	Species, Strain, Sex, No/group	Average score 24, 48, 72 h		Reversibility yes/no	Results	Remarks	Reference
		Erythema	Oedema				
OECD 404	Rabbit, NZW 3M+3F	0-0-0	0-0-0	Not applicable	Not irritating	Vehicle: propylene-glycol + saline (ratio 70/30 v/v)	Ullmann, L. (1980); report no 800558,

5.3.2 Eye

Penconazole instillation into rabbit eyes (100 mg/eye) was followed by slight ocular irritation, never exceeding a severity score of 1. Effects (conjunctival redness) were still notable after 7 days in some animals. Recovery was complete after 10 days.

Table 5.3-2: Summary of eye irritation

Method/ Guideline	Species, Strain, Sex, No/group	Average Score 24, 48, 72 h				Reversi-bility yes/no	Results	Remarks	Reference
		Cornea	Iris	Redness Conjunc-tiva	Chemo-sis				
OECD 405	Rabbits, NZW 3M + 3F	0.67-0.83-0.83	1-0-0.17	1-1-1	1-1-0.33	Not applicable	Not irritating	None	Kuhn, J. (1988); report no 5303-88

5.3.3 Respiratory tract

No data are available.

5.3.4 Summary and discussion of irritation

Penconazole is not irritating to the skin but produced slight eye irritation in rabbits. However, the severity of the response does not meet the criteria for classification laid down in Council Directive 67/548/EEC or regulation (EC) 1272/2008.

5.4 Corrosivity

In skin and eye irritation studies there was no evidence for a corrosive action of penconazole.

5.5 Sensitisation

5.5.1 Skin

Intradermal injection of penconazole tech. in peanut oil caused erythema and oedema (grade 1) at concentrations of 0.5, 1.0, 3.0 and 5.0 %. When administered epidermally in vaseline, penconazole caused erythema (but no oedema) at concentrations of 30 % and 50 %, but not at 10 or 20 %. After challenge application, skin reactions were evident at the application site in some animals at the 24 and 48 h time points.

Table 5.5-1: Summary of skin sensitisation

Method/ Guideline	Species, Strain, Sex, No/group	Number of animals sensitised/Total number of animals	Results	Remarks	Reference
OECD 406 GPMT	Guinea pig, GOHI Himalayan Spotted 10M+10F (treated) 5M+5F (control)	0/10 (control) 3/20 (treated)	Not sensitising	Vehicle: intradermal induction: peanut oil; topical induction and challenge: vaseline	Cantoreggi, S. (1998); report no. 983118,

5.5.2 Respiratory system

No data are available.

5.5.3 Summary and discussion of sensitisation

Penconazole induced less than 30 % positive responses in the skin sensitisation test in Guinea pigs (maximisation test). No classification is required.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

In all three species investigated, rat, mouse and dog, the liver was the main target organ following oral administration of penconazole. In addition, some evidence for a disturbance of protein and lipid metabolism was found. Histopathological evidence for organ toxicity, described as being of minimal severity, was accompanied by reductions in body weight gain and food consumption.

Table 5.6-1: Summary of oral repeat dose toxicity

Method/ Guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels ppm (mg/kg bw /d)	NO(A)EL ppm (mg/kg bw /d)	LO(A)EL ppm (mg/kg bw /d)	Results, Main effects/ Target organs	Remarks	Reference
OECD 407	Oral/ gavage, 28 days	Rat, Tif:RAIf; 10M+10F	(0-20/100-100/500-500/1000)	20 < 100	100 < 500	Bw gain↓; water consumption ↑ (F); ALT, AP, bilirubin, protein ↑; liver: weight ↑, hepatocellular hypertrophy; kidney: weight ↑, urine volume ↑; adrenal: weight ↑; thyroid: weight ↑	Vehicle: aqueous 0.5% carboxy-methyl-cellulose, 0.1% Tween 80 Doses increased on study day 8	Basler, W. (1984); report no 820822
OECD 407	Oral/ gavage, 28 days	Rat, Tif:RAIf; 10M+10F	(0-100-500)	< 100	100	Platelets ↑; ALT, bilirubin, protein ↑, prothrombin time ↓; liver: weight ↑, hepatocellular hypertrophy; kidney: weight ↑; adrenal gland: weight ↑, cortical atrophy (F); thyroid: weight ↑	Vehicle: aqueous 0.5% carboxy-methyl-cellulose, 0.1% Tween 80	Fankhauser H. (1991); report no 901026

Method/ Guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels ppm (mg/kg bw /d)	NO(A)EL ppm (mg/kg bw /d)	LO(A)EL ppm (mg/kg bw /d)	Results, Main effects/ Target organs	Remarks	Reference
OECD 408	Oral/diet 90 days	Rat, Tif:RAIf; 20M+20F	0-30-300-3000 (M: 0-2.0-19.4-202; F: 0-2.1-20.7-209)	300 (M: 19.4; F: 20.7)	3000 (M: 202; F: 209)	Bw gain ↓; protein ↑; liver: weight ↑, hepatocellular hypertrophy; urea nitrogen ↑	None	Basler, W. (1982); report no 801194
OECD 408	Oral/diet 90 days	Rat, Tif:RAIf; 20M+20F	0-10-30-100 (M: 0-0.8-2.1-7.1; F: 0-0.8-2.1-7.3)	100 (M: 7.1; F: 7.3)	> 100 (M: > 7.1; F: > 7.3)	Protein ↑	None	Basler, W. (1983); report no 821054
OECD 408	Oral/diet 90 days	Rat, Crl:CD(SD)BR 15M+15F	0-10-100-300-500-1000-2400 (M: 0-0.8-7.5-23.2-37.5-72-179; F: 0-1.0-9.8-28.3-45.2-86-209)	300 (M: 23.2; F: 28.3)	500 (M: 37.5, F: 45.2)	Bw gain ↓(F); liver: weight ↑ (M), hepatocellular vacuolisation, hypertrophy, degeneration		Hiles, R. (1987); report no. HLA 6117-120
OECD 408	Oral/diet 90 days	Mouse, Crl:CD-1(ICR)BR 15M+15F	0-10-100-300-500-1000-2400 (M: 0-1.7-17.1-51.8-84.7-163-423; F: 0-2.5-23.9-72.2-115.6-237-614)	M: 300 (52) F: 1000 (237)	M: 1000 (85) F: 2400 (614)	Bw gain ↓; liver: weight ↑, hepatocellular hypertrophy, vacuolisation, degeneration	None	Hiles, R. (1987); report no. HLA 6117-121
OECD 408	Oral/diet 90 days	Mouse, C57BL/10JfCD-1 10M+10F	0-100-500-1500-3000-5000 (M: 0-14-69-229-437-837; F: 0-18-87-274-545-983)	500 (M: 69 F: 87)	1500 (M: 229; F: 274)	Bw gain ↓; liver: weight ↑, hepatocellular hypertrophy	None	Milburn, G. (2002); report no. CTL/PM1235
OECD 409	Oral/diet 90 days	Dog, Beagle 4M+4F	0-100-500-5000/2500 (90-d M: 0-3.3-17.5-133; F: 0-3.8-18-139)	100 (M: 3.3 F: 3.8)	500 (M: 17.5; F: 18)	Bw gain ↓; liver: weight ↑, hepatocyte necrosis	None	Gfeller, W. (1984); report no. 801187
OECD 409	Oral/diet 1 year	Dog, Beagle 4M+4F 2M+4F for recovery	0-100-500-5000/2500 (M: 0-3.1-16.9-133/85.9; F: 0-3.3-16.7-139/88.9)	100 (M: 3.1 F: 3.3)	500 (M: 16.9; F: 16.7)	Bw gain ↓; liver: weight ↑, hepatocyte necrosis, inflammation, fibrosis	4-week recovery period 5000 ppm reduced to 2500 ppm from week 20	Gfeller, W. (1984); report no. 801187

5.6.2 Repeated dose toxicity: inhalation

No data are available. Based on the results of the acute toxicity study, a repeated dose inhalation toxicity study has not been required.

5.6.3 Repeated dose toxicity: dermal

Repeated dermal application of penconazole moistened with water to rabbits at dose levels up to 2000 mg/kg bw/d over a 21-day period was well tolerated without any signs of overt toxicity.

Table 5.6-2: Summary of dermal repeat dose toxicity

Method/ Guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels mg/kg bw/d	NO(A)EL mg/kg bw/d	LO(A)EL mg/kg bw/d	Results, Main effects/ Target organs	Remarks	Reference
OECD 410	Dermal, 21 days	Rabbit, NZW; 5M+5F	0-1000-1500-2000	2000	> 2000	None	Vehicle: Moistened with water, low solubility	Seifert, G. (1983); report no 820206.

5.6.4 Other relevant information

No other relevant information is available.

5.6.5 Summary and discussion of repeated dose toxicity:

The dog was the most sensitive species with a NOAEL of 100 ppm (about 3 mg/kg bw/day), based on reduced body weight gain and hepatotoxicity observed in the combined 90-day/1-year study. The overall subchronic NOAEL for rats derived from three 90-d feeding studies was 300 ppm (ca. 25 mg/kg bw/day), which was also consistent with the results from two 28-day gavage tests. This NOAEL was based on signs of hepatotoxicity (increased liver weight associated with histopathological alterations, raised serum transaminase and AP levels) as well as clinical chemistry changes at dose levels of or above 100 mg/kg bw/day. Mice were less sensitive with a NOAEL of 500 ppm (equivalent to 69/87 mg/kg bw/day for males and females, respectively). The liver changes are considered mainly a response to the increased metabolic load. Repeated dermal application of penconazole to rabbits at dose levels up to 2000 mg/kg bw/d over a 21-day period was well tolerated without any signs of overt toxicity. The NOAEL for systemic toxicity was therefore higher than 2000 mg/kg bw/day. No classification for repeated dose toxicity is required.

5.7 Mutagenicity

5.7.1 In vitro data

Penconazole did not induce gene mutations in bacterial (using *S. typhimurium strains* and *E. coli* WP2) or mammalian cells (Chinese hamster V79 cells) in vitro. An in vitro chromosome aberration test in CHO cells was negative with respect to clastogenicity, and penconazole did not induce unscheduled DNA synthesis in primary rat hepatocytes in vitro.

Table 5.7-1: Summary of in vitro mutagenicity

Method/ Guideline	Test system (Organism, strain)	Concentra-tions tested (give range)	Results		Remarks give information on cytotoxicity and other	Reference
			+ S9	- S9		
OECD 471	*S. typhimurium*: TA1535, TA1537, TA98, TA100	0-2560 µg/plate	Negative	Negative	Cytotoxicity at 2560 µg/plate	Deparade, E. (1984); report no. 830750
OECD 471	*S. typhimurium*: TA1535, TA1537, TA98, TA100, T102 *E. coli*: WP2PuvrA	0-2000 (*S. typhimurium*) 0-5000 (*E. coli)* µg/plate	Negative	Negative	None	Deparade, E. (1999); report no. 983114
OECD 473	Chinese hamster ovary (CHO) cell line CCL 61	0-50 µg/mL	Negative	Negative	Cytotoxicity at 50 µg/mL	Ogorek, B. (1999); report no. 983116
OECD 476 (Forward mutation)	Chinese Hamster Cells V79	0-80 µg/mL	Negative	Negative	Cytotoxicity at 80 µg/mL	Ogorek, B. (1999); report no. 983115
Similar to OECD 482 (DNA repair)	Primary rat hepatocytes	0-40 µg/mL	Negative	Negative	Cytotoxicity at > 40 µg/mL	Puri, E. (1984); report no. 811522

5.7.2 In vivo data

A bone marrow micronucleus test in mice revealed no evidence for clastogenic or aneugenic activity of penconazole in vivo.

Table 5.7-2: Summary of in vivo mutagenicity

Method/ Guideline	Species, Strain, Sex, No/group	Route, Frequency of application	Sampling times	Dose levels mg/kg bw	Results	Remarks	Reference
OECD 474 (Micronucle-us assay)	Mouse, ICO:CD1(CRL) 5M+5F	Oral, single dose	24, 48 hours	M: 0-200-400-800; F: 0-125-250-500	Negative	Vehicle: aqueous 0.5% carboxy-methyl-cellulose	Deparade, E. (1999); report no. 983117

5.7.3 Human data

No data are available.

5.7.4 Other relevant information

No other relevant information is available.

5.7.5 Summary and discussion of mutagenicity

Penconazole was negative in all mutagenicity tests performed. Tested *in vitro*, it induced neither gene mutations in bacterial or mammalian cells (Chinese hamster), nor chromosome aberrations in CHO cells, nor unscheduled DNA synthesis in rat hepatocytes. Furthermore a bone marrow micronucleus test revealed no evidence for clastogenic or aneugenic activity *in vivo*. It was concluded that penconazole had no genotoxic potential. Classification for genotoxicity is not required.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

In the 2-yr study in rats, only a slight increase in both absolute and relative liver weight was observed in females at and above 150 ppm. This was, however, not correlated with any biochemical or histological findings. In mice, administration of penconazole resulted in a clear body weight reduction at 1500 ppm in males and females. Liver weight was increased in males by 27 % and in females by 5 % while spleen weight was slightly reduced. Histopathologically, the liver demonstrated an increased incidence and severity of hepatocyte vacuolation. Penconazole treatment did not affect tumour incidence or survival.

Table 5.8-1: Summary of oral carcinogenicity

Method/ Guideline Route of exposure	Route of exposure, duration	Species, Strain, Sex, No/group	Dose levels ppm (mg/kg bw/d)	Results Main effects/ Target organs/ Tumors	NO(A)EL ppm (mg/kg bw/d)	LO(A)EL ppm (mg/kg bw/d)	Remarks	Reference
OECD 453	Oral/diet 52 weeks 104 weeks 116/117 weeks	Rat, Tif: RAIf (SPF) 10M+10F 20M+20F 50M + 50F	0-5-75-150-300 (M: 0-0.3-3.8-7.3-15.3; F: 0-0.3-4.0-8.1-16.6)	No relevant toxicity	300 (M: 15.3; F: 16.6)	> 300 (M: > 15.3; F: > 16.6)	None	Basler, W. (1985); report no. 811415
OECD 451	Oral/diet 80 weeks	Mouse, C57BL/10Jf CD-1 50M + 50F	0-25-200-1500 (M: 0-2.7-21.7-178; F: 0-3.5-28.2-222)	Bw gain ↓; liver: weight ↑, hepatocyte vacuolation	200 (M: 21.7; F: 28.2)	1500 (M: 178; F: 222)	None	Milburn, G. (2004); report no. CTL/PM1239
OECD 453	Oral/diet 52 weeks 104 weeks 106/107 weeks	Mouse, Tif:MAGf (SPF) 10M+10F 20M+20F 50M + 50F	0-5-75-150-300 (M: 0-0.8-9.8-19.3-40.8; F: 0-0.7-8.8-17.2-35.7)	No relevant toxicity	300 (M: 40.8; F: 35.7)	> 300 (M: > 40.8; F: > 35.7)	None	Basler, W. (1985); report no. 811414

5.8.2 Carcinogenicity: inhalation

No data are available.

5.8.3 Carcinogenicity: dermal

No data are available.

5.8.4 Carcinogenicity: human data

No data are available.

5.8.5 Other relevant information

No other relevant information is available.

5.8.6 Summary and discussion of carcinogenicity

The oral NOAEL for the rat was the highest dose tested, i.e. 15 mg/kg bw/day. Penconazole induced hepatotoxic effects and body weight reductions in mice at a dose of 1500 ppm. The NOAEL for this species is 36 mg/kg bw/day. No evidence was found for a carcinogenic potential of penconazole in rats or mice up to dose levels of 300 ppm in rats and 1500 ppm in mice. Classification for carcinogenicity is not required.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

Adult toxicity in the 2-generation studies was comparable to the result of other repeat dose studies The liver was the main target organ. Mating and fertility were not impaired. Pregnant females in one of the two studies showed a shift towards longer pregnancy duration at 2000 ppm (200 mg/kg bw/day) and a small number suffered from dystocia and died during or after parturition. The perinatal mortality in the offspring, mostly presenting as total litter losses, reflects the prolonged parturition process. No similar effect was observed in the second study at slightly higher dose levels with a material of greater purity, except for a very slight increase in the number of high dose females with at least one stillborn pup. The NOAEL for reproductive parameters, the parents and the offspring was 30 mg/kg bw/day.

Table 5.9-1: Summary of effects on fertility

Method/ Guideline	Route of exposure	Species, Strain, Sex, No/group	Dose levels ppm	Critical effect Parental, Offspring (F1, F2)	NO(A)EL Parental toxicity ppm (mg/kg bw/d)	NO(A)EL reproductive toxicity ppm (mg/kg bw/d)	NO(A)EL offspring toxicity ppm (mg/kg bw/d)	Reference
Similar to OECD 416	Oral/diet	Rat, Tif:RAIf(SPF), 20M+20F	0-80-400-2000	P: bw gain ↓, food ↓; liver wt ↑; pregnancy duration ↑, dystocia ↑ F1, F2: perinatal mortality ↑; bw gain ↓; liver wt ↑, hepato-cellular hypertro-phy	400 (M: 30; F: 40)	400 (40)	400 (40)	Fritz, H.. (1983); report no. 811416
OECD 416	Oral/diet	Rat, Crl:COBS CD 30M+30F	0-25-250-2500	P: bw gain ↓ (F), food ↓ F1, F2: perinatal mortality ↑; bw gain ↓	250 (30)	250 (30)	250 (30)	Schardein, J. (1987); report no. 382-119

5.9.2 Developmental toxicity

In the rat studies, maternal toxicity occurred at doses above 100 mg/kg bw/day and consisted of decreased food consumption and body weight gain as well as clinical signs and mortalities from gastro-intestinal lesions.The embryotoxicity at the same dose levels manifested as prenatal lethality, slight delay in growth and skeletal development and a slight increase in the occurrence of cervical ribs at 300 mg/kg bw/day. The resulting maternal and developmental NOAEL was 100 mg/kg bw/day.

In the rabbit, doses of more than 75 mg/kg bw/day resulted in reduced maternal food consumption and a lower body weight gain or body weight loss. High dose foetuses in the first study showed no toxicity except slightly increased incidences of bilateral microphthalmia and internal hydro-cephalus. Additional historic control data showed the microphthalmia incidence to be within the control range of the laboratory. Neither finding was reproducible in a second study with a higher dose level and a test material of higher purity. A very slight reduction in foetal weight was noted in the high dose but in combination with a lower litter size (unrelated to penconazole) which may have compensated in part for a treatment-induced growth retardation. The overall NOAEL for maternal and developmental toxicity was 75 mg/kg bw/day.

Table 5.9-2: Summary for developmental toxicity

Method/ Guideline	Route of exposure, Duration	Species, Strain, No/group	Dose levels mg/kg bw	Critical effects 1) dams 2) fetuses	NO(A)EL Maternal toxicity mg/kg bw/d	NO(A)EL Teratogenicity Embryotoxicity mg/kg bw/d	Remarks	Reference
Similar to OECD 414	Oral, pregnancy day 6-15 pregnancy day 10-14	Rat, Tif:RAIf (SPF) 25F 15F	0-30-100-300 0-300-450	1) Bw gain ↓, food ↓; mortality ↑ 2) Bw ↓; skull and limb ossification ↓	100	100	Vehicle: aqueous 2 % carboxy-methyl-cellulose	Fritz, H.. (1981); report no. 800549
OECD 414	Oral, pregnancy day 6-15	Rat, Crl:CD(SD) 25F	0-5-100-500	1) Bw gain ↓, food ↓; clinical signs ↑, mortality ↑ 2) Embryo-lethality ↑; bw ↓; cervical and 14th ribs ↑	100	100	Vehicle: corn oil	Salamon, C. (1985); report no. 450-2087
OECD 414	Oral, pregnancy day 6-18	Rabbit, Chinchilla 20F	0-25-75-150	1) Bw gain ↓, food ↓ 2) Internal hydrocephalus 2/125 foetuses, 2/16 litters	75	75	Vehicle: aqueous 0.5 % sodium carboxy-methyl-cellulose	Giese, K. (1982); report no. 811354
OECD 414	Oral, pregnancy day 7-19	Rabbit, NZW 20F	0-10-50-200	1) Food ↓; bw loss 2) Bw ↓	50	50	Vehicle: 3 % aqueous corn starch	Nemec, M. (1985); report no. WIL-82004

5.9.3 Human data

No data are available.

5.9.4 Other relevant information

The toxicological profile observed in the reproductive toxicity studies with penconazole in rats (gastro-intestinal lesions, maternal mortality, prolonged pregnancy duration and dystocia) is very similar to the findings with the non-steroidal antiphlogistic drug piroxicam in pregnant rats and guinea pigs and in rat foetuses (Welsh, T. et al., 2005; Burdan, F., 2005; Burdan F. et al., 2004). Piroxicam inhibits prostaglandin-endoperoxide synthase 1 (PTGS1, Cox-1), the key enzyme in prostaglandin biosynthesis, resulting in prostanoid deficiency and reduced prostaglandin receptor signaling in various tissues. Penconazole toxicity on the arachidonic acid pathway is supported by the finding that other triazoles fungicides (myclobutanil, propiconazole, triadimefon) can induce changes in rat liver genes associated with this pathway, specifically the prostaglandin E receptor 3

(Goetz, A.K., Dix D.J., 2009a; Goetz, A.K., Dix D.J., 2009b). Ptger3 (EP3) is involved in the stimulation of duodenal bicarbonate secretion in rats (Takeuchi, K. et al., 1999) and mediates inhibition of acid secretion in gastric mucosa cells (Coleman, R.A. et al, 1994). Its down-regulation by high, repeated intragastric doses of penconazole would explain the gastro-intestinal toxicity in pregnant females. Ptger3 also has contractile activity and is much stronger expressed in the uterus than in the liver (Brodt-Eppley, J., Myatt, L., 1998; Sugimoto, Y., Narumiya, S., 2007). The receptor is one among several contractile-associated proteins in the uterus and could be involved in the prolongation of pregnancy/dystocia seen in one rat study at a dose of about 200 mg/kg bw/day. The luteolytic function of prostaglandin receptors in the ovary is required for the initiation of parturition in rodents but not in the human where progesterone production shifts from the corpus luteum to the placenta early in pregnancy.

Based on the fact that dystocia which occurred at a high dose in the first but not in the second two-generation study with penconazole has been seen with other triazoles as well, the draft EFSA Scientific Report (2008) on the Peer Review of Penconazole, proposed that a classification as **Xn; R62 (Possible risk of impaired fertility)** should be considered. In addition, a classification of **Xn; R63 (Possible risk of harm to the unborn child)** was proposed based on cervical ribs in rat foetuses in the maternally lethal dose range and on microphthalmia in rabbits.

5.9.5 Summary and discussion of reproductive toxicity

Penconazole did not affect male or female fertility. At high doses which also reduced maternal body weight gain, pregnancy and/or parturition were prolonged in one study with dystocia occuring in a few dams. From the toxicological profile at high doses there is some evidence that an effect on the arachidonic acid-prostaglandin signaling pathway could be involved. The effect was not reproducible in a second study using material of higher purity. Differences in rat strain sensitivity or the presence of contaminants have not been further elucidated. However, the finding of dystocia which only occurs in pregnant animals would not warrant a classification for fertility impairment.

In rats, embryotoxicity was observed in the maternally lethal dose range, manifesting as postimplantation loss, retarded skull ossification and increased incidence of cervical ribs. . In the rat penconazole is metabolised to 1,2,4-triazole, a compound known to be teratogenic at high doses. However, the amount of this metabolite in penconazole treated animals appears to be below the threshold for teratogenicity. This is indicated by the profile of foetal abnormalities induced by 1,2,4-triazole (cleft palate, undescended testes, hydronephrosis) which does not match the findings in conceptuses exposed to penconazole. A slight increase of malformations could not be confirmed in rabbits when a material of higher purity was used. While a relationship to the test substance cannot be completely excluded it appears unlikely when considering the low incidence and the lack of reproducibility. A classification for fertility effects or developmental toxicity is not required.

5.10 Other effects

Neurotoxicity

The available data package on penconazole gives no indication for any neurotoxic potential of the compound. No special examinations on neurotoxicity were therefore conducted.

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

Penconazole (technical) is not explosive in the sense of EEC method A14.

6.2 Flammability

Penconazole (technical) not highly flammable in the sense of EEC method A10.

6.3 Oxidising potential

Penconazole (technical) has no oxidising properties in the sense of EEC method A17.

7 ENVIRONMENTAL HAZARD ASSESSMENT

The environmental hazard assessment for Penconazol is based on the Draft Assessment Report and Proposed Decision of Germany prepared in the context of the possible inclusion of Penconazol in Annex I of Council Directive 91/414/EEC (DAR June 2007 + Final addendum July 2008, RMS Germany). – see IUCLID 5 dossier, chapter 13

Tests made according the EPA guideline are comparable with tests made according OECD guidelines and only available.

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

The acute toxicity of penconazole to fish is summarised in Table 7.1-1

Table 7.1-1: Acute toxicity of penconazole to fish

Guideline/ Test method	Species	Exposure		Results		Reference Report No. Doc ID
		Design	Duration (h)	Endpoint	Value (mg/L)	
US EPA (1975); Series 660/3-75-009	*Oncorhynchus mykiss*	Static	96	LC_{50}	1.3 mm[1)]	Surprenant D.C. (1984) BW-84-5-1583 WAT 2004-799
US EPA (1975); Series 660/3-75-009	*Ictalurus punctatus*	Static	96	LC_{50}	2.8 mm[1)]	Surprenant D.C. (1984) BW-84-5-1582 WAT 96-50110
US EPA (1975); Series 660/3-75-009	*Lepomis macrochirus*	Static	96	LC_{50}	2.8 mm[1)]	Surprenant D.C. (1984) BW-84-5-1584 WAT 2004-798
OECD 203	*Cyprinus carpio*	Static	96	LC_{50}	3.8 nom	Rufli H. (1984) 840736

						WAT 2004-1100

[1)] mm … mean measured

Long-term toxicity to fish

The long term toxicity of penconazole to fish is summarised in Table 7.1-2

Table 7.1-2: Long-term toxicity of penconazole to fish

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (d)	Endpoint	Value (mg/L)	
Internal method	*Pimephales promelas*	flow trough	30	NOEC	0.36 mm[1)]	Surprenant D.C. (1984) BW-84-7-1600 WAT 96-50111

[1)] mm … mean measured

Azole fungicides are known to be potential inhibitors of sterol 14-alpha-demethylase and aromatase and therefore may affect the endocrine system (Zarn, J.A., Brüschweiler, B.J. and Schlatter, J.R., EHP 2003, 111(3):255 - 61); AVS 2006-263. Ecologically relevant effects associated with endocrine disruption could remain undetected in the prolonged fish tests if no parameters specific for the endocrine system were investigated. This concern about a relevant endocrine potential of penconazole is also expressed in the working document of the EU Commission on the implementation of the community strategy on endocrine disruptors (EU Commission, 2004) where penconazole was classified as ”HPV and/or persistent and/or exposure expected in humans and wildlife, with insufficient data”

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

The acute toxicity of penconazole to invertebrates is summarised in Table 7.1-3.

Table 7.1-3: Acute toxicity of penconazole to invertebrates

Guideline/ Test method	Species	Exposure		Results		Reference Report No. Doc ID
		Design	Duration (h)	Endpoint	Value (mg/L)	
US EPA (1975); Series 660/3-75-009	*Daphnia magna*	Static	48	EC_{50}	6.75 nom	Hitz H.R. (1981) 810763

						WAT 96-50107

Long-term toxicity to aquatic invertebrates

The long-term toxicity of penconazole to invertebrates is summarized in Table 7.1-4.

Table 7.1-4: Long-term toxicity of penconazole to invertebrates

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (d)	Endpoint	Value (mg/L)	
Internal method similar to US EPA (1975); Series 660/3-75-009	*Daphnia magna*	flow trough	21	NOEC	0.069 mm[1)]	Surprenant D.C. (1984) BW-84-8-1614 WAT 96-50108

[1)] mm … mean measured

7.1.1.3 Algae and aquatic plants

The toxicity of penconazole to algae and aquatic plants is summarised Table 7.1-5

Table 7.1-5: Long-term toxicity of penconazole to algae and aquatic plants

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (h)	Endpoint	Value (mg/L)	
OECD 201	*Pseudokirchneriella subcapitata (Selenastrum capricornutum)*	Static	96	E_rC_{50}	4.9 mm[1)]	Desjardins D.K. et al. (2001) 528A-112 WAT 2004-1105
US EPA (1980) [2)]	*Lemna gibba*	Static	14 d	E_rC_{50}	0.22 nom	Hughes J.S. (1985) MPI-267-22-1100-2 WAT 96-50112

[1)] mm … mean measured

[2)] US EPA Proposed Guidelines for Registering Pesticides in the United States, Subpart J, 1980; Holst RW and TC Ellwanger, 1982

The study with the aquatic plant *Lemna gibba* was more sensitive than the study with algae *Pseudokirchneriella subcapitata*. Therefore this study can be regarded as the key study for the aquatic toxicity of penconazole and hence for classification and labelling. The duration of tests with higher aquatic plants always is longer than with algae. In this case the result based on the EPA guideline, which can be compared with the result of the OECD 201.

The study can be regarded as the key study and is presented in more detail below:

Toxicity of penconazol to *Lemna gibba*

Author:	Hughes, JS. (1985); WAT 96-50112
Title:	The toxicity of CGA 71818, Lot. No. FL-830634 to *Lemna gibba* G3 (duckweed). Malcolm Pirnie Inc., White Plains, New York. Unpublished report no. MPI-267-22-1100-2
Date:	13 to 27 July 1984
Doc ID:	Syngenta file No. CGA71818/0082
Guidelines:	US EPA Proposed Guidelines for Registering Pesticides in the United States, Subpart J, 1980; Holst RW and TC Ellwanger, 1982
Deviations:	None
GLP:	Yes
Validity:	Acceptable

Materials and methods:

Test material: Technical CGA 71818, batch number FL-830634, purity 87.3 %.

The potential toxicity of penconazole to the duckweed, *Lemna gibba*, was investigated in a static test where cultures were exposed to 5 nominal concentrations (0.05, 0.1, 0.2, 0.4 and 0.8 mg/L) of technical penconazole for 14 days. Aliquots of a penconazole stock solution prepared in acetone were added to *Lemna* cultures consisting of 4 colonies, each with 4 fronds, in nutrient medium. The test incorporated three replicate cultures for each dose, four replicate cultures of a solvent control prepared with acetone (0.8 mL/L) and four replicates of an untreated control. Cultures were maintained for 14 days under constant conditions of 25 $\pm$2 °C and 5000 - 7000 lumens/m^2. Frond counts were made on days 3, 4, 5, 6, 7, 10, 11, 12 and 14, and dry frond weight was determined at 14 days. Test solution pH was measured every 3 days.

Findings:

Test solution pH ranged from 4.8 – 6.0. The effects of penconazole on frond number and dry weight are presented in the following table.

Table 7.1-6 Effect of penconazole on frond production in *Lemna gibba.*

Nominal concentration (mg/L)	14 day frond number		14 day dry weight (mg)	
	Total	% Reduction versus control [a]	Total	% Reduction versus control [a]
Solvent control	565	-	93.9	-
0.05	588	- 4.1	106.5	- 13.4
0.1	608	- 2.6	109.4	- 16.5
0.2	382	32.4	34.6	63.2
0.4	24	95.8	4.2	95.5
0.8	16	97.2	4.7	95.0

[a] A negative % reduction indicates a value higher than the control.

Conclusion

Based on nominal concentrations, the 14-day EC_{50} values for frond number and dry weight were 0.22 and 0.11 mg/L, respectively. The test concentration was not analytically confirmed.

7.1.1.4 Sediment organisms

The toxicity of penconazole to sediment dwelling organism is summarised in Table 7.1-7.

Table 7.1-7: Long-term toxicity of penconazole to *Chironomus sp.*

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (d)	Endpoint	Value (mg/L)	
OECD (1998) [1)]	*Chironomus riparius*	a) Static, spiked water	28	NOEC (emergence / development)	2.0 nom (0.8 initial measured conc.)	Grade (1999) 983757 WAT 1999-807
	Chironomus riparius	b) Static, spiked sediment	28	NOEC (emergence / develoment)	25.2 mg/kg nom	

[1)] OECD Guideline for testing of chemicals, Proposal for Toxicity Test with Chironomidae, May 1998

7.1.1.5 Other aquatic organisms

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Not relevant for this type of dossier.

7.2 Terrestrial compartment

Not relevant for this type of dossier.

7.3 Atmospheric compartment

Not relevant for this type of dossier.

7.4 Microbiological activity in sewage treatment systems

Not relevant for this type of dossier.

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Not relevant for this type of dossier.

7.6 Conclusion on the environmental classification and labelling

Penconazole is hydrolytically stable. Penconazole was found to be not readily biodegradable within 28 days in the Sturm test (OECD guideline 301B).

Penconazole has a log Kow of 3.72. In a bioconcentration study, a steady state BCF value of 200 was obtained based total radioactive residue in whole fish and average total radioactive residue in water.

Penconazole is acute toxic to fish and invertebrates as indicated by the LC50 values between 1.3 and 4.3 mg/L obtained with four fish species and an EC50 value of 6.75 mg as/L for invertebrates. The toxicity of penconazole to algae is ErC_{50} = 4.9 mg/L and to aquatic plants ErC_{50} = 0.22 mg/L. The lowest endpoints in long- term studies were observed with invertebrates (21-d reproduction study NOEC = 0.069 mg/L) and fish (30-d early-life-stage study NOEC = 0.36 mg/L). However, this test is not sufficient to fully address possible ecologically relevant effects associated with endocrine disruption in fish which is known to be relevant for other members of the group of DMI fungicides. Because the magnitude of the endocrine potential in fish is not fully known there exists a higher uncertainty regarding the long-term endpoint for fish.

Conclusion of environmental classification according to Directive 67/548/EEC

In aquatic toxicity studies, ErC_{50} value for aquatic plants was < 1 mg/L. Penconazole is not readily biodegradable according to the Sturm test (OECD 301B). Considering the results of the test on ready biodegradability and levels of mineralisation in the simulation study, penconazole is considered not rapidly biodegradable (a degradation of >70% degradation within 28 days) for purposes of classification and labeling. Penconazole has a log Kow of 3.72. The experimentally derived steady state BCF of 200 (based on total radioactive residue for whole fish) is above the trigger of 100 (criterion for bioaccumulating potential conform Directive 67/548/EEC) for not rapidly biodegradable substances. Penconazole therefore fulfils the criteria for classification with N; R50-53.

Based on the toxicity data for the aquatic plant *Lemna gibba* (ErC50 of 0.22 mg/L) in a 14-day static study the following specific concentration limits should be applied:

Concentration	Classification
$C \geq 25\%$	N; R50-53
$2.5\% \leq C < 25\%$	N; R51-53
$0.25\% \leq C < 2.5\%$	R52-53

Where C is the concentration of penconazole in the preparation.

Conclusion of environmental classification according to Regulation EC 1272/2008

In aquatic toxicity studies, ErC_{50} value for aquatic plants was < 1 mg/L. Penconazole is not readily biodegradable according to the Sturm test (OECD 301B). Considering the results of the test on ready biodegradability and levels of mineralisation in the simulation study, penconazole is considered not rapidly biodegradable (a degradation of >70% degradation within 28 days) for purposes of classification and labeling. The experimentally derived steady state BCF of 200 (based on total radioactive residue for whole fish) is lower then 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008) for not rapidly biodegradable substances. Penconazole therefore fulfils the criteria for classification as aquatic environmental hazard acute category 1, H400 and aquatic environmental hazard chronic category 1, H410.

The M-factor for penconazole is 1. This value is based on ErC_{50} value of 0.22 mg/L obtained for the aquatic plant *Lemna gibba* in a 14-day static study.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Penconazole is an active substance in the meaning of Directive 91/414/EEC and therefore subject to harmonised classification and labelling (Regulation EC 1272/2008 article 36.2).

OTHER INFORMATION

This proposal for harmonised classification and labelling is based on the data provided for the registration of the active substance penconazole according to Directive 91/414/EEC. The summaries included in this proposal are partly copied from the DAR and the final addendum to the DAR. Some details of the summaries were not included when considered not relevant for a decision on the classification and labelling of this substance. For more details the reader is referred to the DAR and its addendum.

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