Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at EU level of

Penconazole

EC number: 266-275-6
CAS number: 66246-88-6

ECHA/RAC/CLH-O-0000002679-61-01/A1

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

11 July 2012

CONTENTS

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

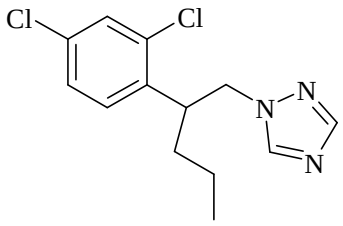
EC Number: 266-275-6

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 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. (ºC)	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.

RAC evaluation of environmental fate properties
RAC evaluation of degradation and bioaccumulation are compiled under environmental hazards at the end of chapter 7.

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)

RAC evaluation of acute toxicity

Summary of Dossier submitter's proposal

The dossier submitter proposed to classify penconazole as Acute Tox. 4 (H302) according to CLP and Xn; R22 (Harmful if swallowed) according to DSD. The classification and labelling proposal for acute toxicity was based on four oral studies, one inhalation and one dermal study. Two out of four acute oral studies on Penconazole were below the 2000 mg/kg bw threshold for classification. A study performed according to a protocol similar to OECD Guideline No. 401 (Bathe, 1980) on male and female rats resulted in the oral LD_{50}s of 1486 and 3831 mg/kg bw /day, respectively. The LD_{50} for male oral exposure is thus below the threshold for classification. Female mortality data from the study were inconclusive because there was no clear dose response relationship. Given the large difference in male and female LD_{50} values, the meaningfulness of a combined (male, female) oral LD_{50} estimate can be questioned.

In another study, performed according to a protocol similar to OECD Guideline No. 401 (Kobel,

1981), the LD_{50} for male and female rabbits were 645 - 1321 mg/kg resulting in combined acute oral LD_{50} of 971 mg/kg.

The dossier submitter's proposal not to classify and label Penconazole for dermal or inhalation toxicity was based on low toxicity in both the acute dermal toxicity study (rat LD_{50} > 3000 mg/kg bw) and the inhalation toxicity study (rat LC_{50} > 4.05 mg/L).

Comments received during public consultation

Several comments supported the dossier submitter's classification and labelling proposal for acute toxicity.

RAC assessment and comparison with criteria

No classification or labelling is required for acute dermal toxicity (rat LD_{50} > 3000 mg/kg bw) or inhalation toxicity (rat LC_{50} > 4.05 mg/l).

Based on the results of the acute oral LD_{50} in rabbits and rats, Penconazole is considered 'harmful if swallowed' and should be classified as Acute tox. 4 – H302 according to Regulation (EC) 1272/2008 and Xn; R22 according to Directive 67/548/EEC. Classification and labelling is not required for acute dermal or inhalation toxicity.

Sedation effects observed in several acute toxicity studies would possibly justify an additional classification for narcotic effects with STOT SE 3 – H336. However, sufficient details, e.g. on severity and duration of effects were not available to assess the need for classification.

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.

RAC evaluation of irritation

Summary of Dossier submitter's proposal

The dossier submitter did not propose classification and labelling for irritation. The justification not to classify was based on one skin irritation (OECD 404) and one eye irritation study (OECD 405) in rabbits.

Comments received during public consultation

One comment supported the dossier submitter's proposal not to classify penconazole for irritation.

RAC assessment and comparison with criteria

Penconazole is not irritating to the skin but produced slight eye irritation in rabbits. However, the low severity of the response (e.g. Redness Conjunctiva average score after 24, 48 and 72 hours was respectively 1, 1 and 1) does not meet the criteria for classification laid down in 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.

RAC evaluation of corrosivity

Summary of Dossier submitter's proposal

Classification for corrosivity was not proposed based on lack of evidence.

Comments received during public consultation

No comments were received on this endpoint.

RAC assessment and comparison with criteria

No data were provided to RAC on this endpoint and no conclusion is made on the classification and labelling.

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.

RAC evaluation of sensitization
Summary of Dossier submitter's proposal Classification for sensitisation was not proposed by the dossier submitter. **Comments received during public consultation** One Member State supported not to classify and proposed to clarify the comparison with the criteria. **RAC assessment and comparison with criteria** According to the Guinea pig maximisation test (OECD Guideline No. 410), Penconazole induced skin sensitisation in 3/20 animals (control = 0/10), which is less than the 30% positive responses required for classification under Directive n°67/548/EEC or regulation (EC) 1272/2008. RAC agrees the data do not warrant classification for sensitization.

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
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

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	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/10J fCD-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.

RAC evaluation of repeated dose toxicity

Summary of Dossier submitter's proposal

The dossier submitter did not propose to classify Penconazole for repeated dose toxicity.

Among the reported repeated dose toxicity studies on rats (three studies), mice (two studies) and dogs (two studies), the dog appeared to be the most sensitive species. In a study conducted according to a protocol similar to OECD guideline No. 409 (Gfeller, 1984), the derived 90-day NOAEL for males and females were 3.1 and 3.3 mg/kg bw/d (100 ppm), respectively. The associated LOAELs of 16.9 and 16.7 mg/kg/d were based on hepatotoxicity effects: Inflammatory cell infiltration, necrosis, clear dose-dependent increase in liver weight. Also, an increase in the activities of alkaline phosphatases γ-GT, AST, and ALT was observed. However, most of these signs were not severe. Furthermore, when incidence is estimated by pooling males and females, the single incidence of necrosis appears to be an isolated case: 1/8 after 90 days, 0/8 after 1 year.

In this study it was also observed in high dose males' group a moderate to marked reduction in spermatogenic activity, characterised by atrophy of the seminiferous epithelium associated with formation of giant cells, and absence of spermatozoa in the epididymis (which contained cellular

debris). However, the 5000-ppm dose is largely above the MTD that was estimated around 2500 ppm. In the lower/intermediate/high dose groups, some decreases in relative gonad weights were also observed, but the observations were inconsistent compared to control: +23%, -4% and -27% for males and -35%, -8%, -16% in females at the 90-day time point. On the other hand, the liver weight increase was clearly dose-dependent: +1, +15, +75% for males and +8, +24, +88% for females.

In a 90-day oral rat study, conducted according to OECD guideline No. 408 and with Penconazole with a purity of 98.7% (Hiles, 1987a), evidence of hepatotoxicity was also found. Observations include dose-related centrilobular hypertrophy of hepatocytes (in males 0/15, 3/15, 12/15 and 15/15 for 300, 500, 1000 and 2400 ppm, weaker in females), hepatocellular degeneration around the central vein, and an increase in the incidence of hepatocytic vacuolisation (in males 0/15, 1/15, 5/15 for 500, 1000 and 2400 ppm, weaker in females). The derived NOAELs for male and female rats were 23.2 and 28.3mg/kg bw/day (300 ppm), respectively. The LOAELs were 37.5 and 45.2 mg/kg bw/day (500 ppm). A very similar picture was also observed in mouse liver: dose-dependent increase in absolute and relative liver weight (statistically significant from 500 pmm in males and 2400 in females), centrilobular hypertrophy of hepatocytes (in males 0/15, 3/15, 6/15 and 14/15 for 300, 500, 1000 and 2400 ppm), hypertrophic hepatocytes around the central vein with some vacuolar (2400 ppm, males only) (Hiles, 1987b, according to guideline similar to OECD guideline No. 408).

Comments received during public consultation

France commented that some severe liver changes are noted at 500 ppm in dog studies (necrosis in 1 male out of 4 in the 90-day study and fibrosis in the 1-year study) and hepatic degeneration is also observed in one rat 90-day study at 1000 ppm (72 mg/kg bw/d) and the effective dose level of 500 ppm (16.9-18 mg/kg bw/d) is below the guidance value. Based on this France proposed to add classification for repeated dose toxicity, i.e. STOT RE. 2 H373 under CLP and R48/22 under DSD.

RAC assessment and comparison with criteria

The reported liver changes can be considered as only adaptive responses to the increased metabolic load. Although some liver changes at 16.9/16.7 (M/F) mg/kg bw/day (500 ppm) in dog studies could be considered as severe, they appear as isolated cases: necrosis in 1 male out of 4 in the 90-day study and also fibrosis in 1 male out of 4 when the study was prolonged to 1-year. A similar interpretation can be made for the hepatic degeneration observed in one rat 90-day study at 72 mg/kg bw/d (1000 ppm). Although the effective dose levels in both dogs and rats are within the $10 < C \leq 100$ mg / kg body weight/day range, RAC's conclusion is that a classification for specific target organ toxicity is not required under Regulation (EC) 1272/2008 or Directive 67/548/EEC.

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.

RAC evaluation of germ cell mutagenicity
Summary of Dossier submitter's proposal The dossier submitter did not propose classification and labelling for mutagenicity. The proposal was based on five in vitro studies and on a micronucleus test (OECD 474) in mouse, which all were reported to give negative results. **Comments received during public consultation** The UK supported no classification for mutagenicity. **RAC assessment and comparison with criteria** Penconazole had no effects in any mutagenicity tests performed. *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 is concluded that classification for genotoxicity is not required for Penconazole.

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.

RAC evaluation of carcinogenicity
Summary of Dossier submitter's proposal Classification and labelling of penconazole for carcinogenicity was not proposed by the dossier submitter. The proposal was based on one study in rats (OECD 453) and two studies in mice (OECD 451 and 453). **Comments received during public consultation** The UK noted that the top dose tested in each carcinogenicity study was low and that the maximal tolerated dose was not achieved in rats. The UK agreed that the available information does not support classification for carcinogenicity. **RAC assessment and comparison with criteria** Three carcinogenicity bioassays have been performed with Penconazole. In two of these studies (Basler 1985a and b), one in rats and one in mice, the highest dose was 300 ppm (equals 15.3 mg/kg bw/d (M) and 16.6 mg/kg bw/d (F) and 40.8 mg/kg bw/d (M) and 35.7 mg/kg bw/d (F) for rats and mice, respectively). No adverse findings, including tumours, were seen in these studies. However, as no toxicity was seen at the top dose, it was concluded that the doses were too low and the studies can only be considered supportive. In the third study in mice (Milburn 2004) a top dose of 1500 ppm, equal to 178 mg/kg bw/d (M) and 222 mg/kg bw/d (F), was used. This dose caused clear toxic effects but no tumours. The negative result of the Milburn 2004 study together with the supportive studies Basler 1985a and b indicates no carcinogenic potential of Penconazole. Therefore, 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.

RAC evaluation of reproductive toxicity
Summary of Dossier submitter's proposal The dossier submitter did not propose classification and labelling for reproductive toxicity. <u>Effects on fertility</u> Two studies on the impact of Penconazole on fertility were reported. The first one, a 2-generation

study in rats (Tif:RAIf(SPF) (Fritz, 1983) was generally consistent with OECD guideline 416. The results of this study indicated slight toxicity of Penconazole at the 2000 ppm level (146 and 166 mg/kg bw/d in males F_0 and F_1, respectively and 202 and 227 mg/kg bw/d in females F_0 and F_1, respectively) for both the F0 and F1 generation: reduction in body weight gain and food consumption during pre-mating and pregnancy. In addition, increased duration of pregnancy or delayed parturition in F0 and F1 dams were associated with maternal death and/or litter loss at birth.

These effects were not seen in the second study conducted in rats (Crl:COBS CD) (Schardein, 1987) according to OECD guideline 416. No effects were noticed on pregnancy duration or pregnancy index. A statistically significant increase in relative gonad weight was considered to be related to reduced body weight.

In the 1-year study in dogs (Gfeller, 1984) (see repeated dose toxicity section) a reduction in spermatogenic activity was observed. This was accompanied by atrophy of the seminiferous epithelium associated with formation of giant cells, and absence of spermatozoa in the epididymis (which contained cellular debris). However, the signs are not considered relevant for classification, as the dose-effect relationship was not clear and was reduced during the recovery period. It was mainly present at the higher dose where systemic toxicity was recorded,, based on the loss of body weight (not only a decrease in weight gain).

Developmental toxicity

Two developmental toxicity studies in rats and two in rabbits were reported, in addition to the two multi-generation studies described above.

In rats, embryotoxicity was observed as retarded skull and limb ossification and as post-implantation loss (Fritz, 1981; according to OECD guideline 414). This study was performed with the doses 0, 30, 100 and 300 mg/kg bw/d, and later a supplementary study was performed with 300 and 450 mg/kg bw/d. Maternal toxicity was seen at the highest doses but this was not sufficiently severe to explain the findings the results (12% decrease in corrected body weight gain, 4 % reduction in food consumption). Doses of 30 and 100 mg/kg bw/d gave neither maternal nor foetal toxicity.

In the second study in rats (Salamon, 1985; according to OECD guideline 414) the original dose selection was 5, 100 and 750 mg/kg bw/d. Due to high toxicity noted early in the study, the top dose was reduced to 500 mg/kg bw/d. At 500 mg/kg bw/d, severe maternal toxicity was also seen, including maternal death, as well as decreased body weight gain (-14%, +3% and -41% for 5, 100 and 500 mg/kg bw/d groups at study end) and food consumption (-6%, -19% and -42% for 5, 100 and 500 mg/kg bw/d on day 6). The effects seen at the top dose were similar to the effects seen in the earlier study, including retarded skull and limb ossification. Although this study may not be useful for establishing the need to classify Penconazole, its findings were consistent with the older study. The low and mid doses caused no toxicity in neither dams nor pups and the high dose resulted in too high maternal toxicity to be conclusive. From the study protocol it seems that no dose range finding study was performed and the rationale behind the selection of doses was not clear.

In a study in rabbits (Chinchilla, 20F) (Giese, 1982, according to OECD guideline 414), microphthalmia (3/125 foetuses from 3/16 litters, two in combination with internal hydrocephalus) were observed at a dose level of 150 mg/kg/day. The incidence of microphthalmia was above the historical control range given in the study report. However, a greater incidence of this finding was

reported in historical control data submitted during the public consultation. A second study in rabbits (Nemec, 1985, OECD guideline 414) was conducted at a slightly higher dose level. In this study maternal toxicity was seen, but no embryotoxic or teratogenic effects.

Comments received during public consultation

Comments from several member states (Denmark, France, UK, Sweden, Spain and Austria) and one company (Syngenta) were received. The following provides an overview of the comments.

Denmark did not agree with the dossier submitter's arguments about the classification concerning reproductive toxicity and their view was that the observed effect was induced by the active substance and therefore penconazole should be classified for effects on sexual function and fertility as Repr. 2 - H361 under CLP (Repr. Cat. 3; R62 under DSD). In addition to this they point out that based on the effects seen in the developmental studies at high dose levels (cervical ribs in rat and microphtalmia in rabbits) penconazole should be classified for developmental toxicity as Repr. 2 - H361 under CLP (Repr. Cat. 3; R63 under DSD).

Syngenta agreed with the dossier submitter's proposal for non-classification of Penconazole for fertility and developmental toxicity. Concerning fertility, Syngenta commented that the observed increase in dam mortality during the post-partum period was observed at the high dose level (2000 ppm) only and that the studies did not provide evidence that these effects are due to dystocia. Concerning developmental toxicity, Syngenta pointed out that increases in the incidence of cervical ribs were linked to marked maternal toxicity. Also, the incidence of bilateral microphthalmia observed in rabbits was higher than in the concurrent control group, but were within the historical control range for the test laboratory and were therefore considered not to be an effect of treatment. See further details in Annex II.

France supported no classification for fertility but warranted classification and labelling for developmental toxicity, i.e. Repr. 2 - H361d under CLP (Repr. Cat. 3; R63 under DSD). However, concerning fertility, the absence of clear data to establish the mechanism of action (mechanistic studies and/or hormonal analysis were lacking) meant that endocrine disruptive effects could not be ruled out. Concerning the developmental toxicity, France added that hydrocephaly is known to be a class effect of triazoles in rabbit. Also, in one of the rat developmental studies, cervical ribs occurrence was increased at the high dose and increased incidences of variations in ribs are also observed with other triazole compounds. Furthermore, one of the main metabolites, 1,2,4-triazole (comprising 15% of the dose given) is currently classified in the EU as: Repr. Cat. 3; R63. Finally, France added that the argument relating to non-reproducible effects with a higher purity material is not acceptable, since the claimed purity of the technical material is 95%.

The UK wanted to have further discussion on classification for fertility and agreed with the dossier submitter that classification for developmental effects is not required.

The UK noted that under CLP, adverse effects on sexual function and fertility include effects on parturition; therefore, the statement that 'the finding of dystocia which only occurs in pregnant animals would not warrant a classification for fertility impairment' should be changed, since it is possible to classify for fertility on the basis of dystocia. The UK also suggested further discussion of the significance of the dystocia findings and their relevance to humans, and a possible classification for fertility, be included, particularly as other triazoles have been reported to induce this effect.

The UK also pointed out that the death of the corpus luteum of rodents leads to a fall in

progesterone levels, whereas a 'functional progesterone withdrawal' in humans is affected by a repression of prostaglandin responsive genes. However, the mechanism of action of the dystocia induction explained in the report pertains to a down-regulation of the prostaglandin E3 receptor by penconazole, which results in reduced uterine contractility. Since prostaglandin E3 is involved in myometrial contractions in humans, this mechanism of action would appear to be relevant to humans as well as rodents.

The UK commented on developmental toxicity by stating that in rats, the possible developmental effects observed were post-implantation loss, retarded bone ossification and an increased incidence of extra ribs. The first two of these effects were probably related to maternal toxicity, although more information in Table 5.9-2 would clarify this association. The third effect, extra ribs, has been reported in studies of other triazole substances. From the information provided on penconazole, it is not clear if these were associated with maternal toxicity, so clarification of this point would be helpful. Uncertainty surrounds the developmental/teratogenic significance of supernumerary ribs, in particular their post-natal reversibility or otherwise. Generally, findings of this nature are not used as evidence for classification. In rabbits, an increased incidence of microphthalmia in one study was stated to be within the historical control range. An increased incidence of hydrocephalus occurred in one rabbit study but not in a second rabbit study or two rat studies that employed higher maximum doses.

Sweden proposed to consider classification of penconazole as Repr. 2 (H361) according to CLP and Repr. Cat. 3; R62 according to DSD. They also recommended considering whether the observed dystocia reported in both rats and rabbits, implantation loss in rats and aspermatogenesis in rats justified classification in Repr. 2. The results are further supported by the findings of histopathological changes in the testes and epididymidis from the 1 yr study in dogs.

Spain reminded that the draft EFSA Scientific Report (2008) proposed a classification of Repr. Cat. 3; R63 and that a classification as Repr. Cat. 3; R62 should be considered. The Spanish CA considered that a classification is warranted for Penconazole as Repr. 2 (H361f) according to CLP and as Repr. Cat. 3 (R62) according to DSD. This view on classification for fertility was based on prolonged gestation, dystocia and increased parturition mortality of dams and pups observed in a two generation study in rats dosed with 200 mg/kg bd/day (Fritz, 1983) and taking into account the new criteria in CLP that considers dystocia an adverse effect on fertility. Although no similar effects were observed in a second study (Schardein, J., 1987), the rat strain used and purity of the test substance were different in that study and this could explain the different results.

Spain considered that classification for Penconazole as Repr. 2 (H361d) was warranted according to CLP and Xn; Repr. Cat. 3 (R63) according to DSD. This view was based on an increased incidence of bilateral microphthalmia and internal hydrocephalus observed in a teratology study in rabbits (Giese 1982), and an increased in the occurrence of cervical ribs at 500 mg/kg bw/d in a teratology study in rats (Salamon 1985). Besides, the formation of 1,2,4-triazole (metabolite classified as Repr. Cat. 3; R63, accounting for 15% of administered dose) also has to be taken into account.

Spain also brought up other scientific evidence supporting classification. For example, the study results on azole and triazole compounds with the same mode of action, as well as the critical role of several CYP enzymes in reproduction, support the classification of penconazole for fertility (Repr. 2 – H361f, CLP and Repr. Cat. 3; R62, DSD) and for development (Repr. 2 – H361d, CLP and Repr. Cat. 3; R63, DSD).

Austria stated that it seems doubtful to consider Repr. Cat 2 (H361f) under CLP and Repr. Cat. 3; R62 under DSD, appropriate. However, Austria concluded that it might be appropriate to consider classification as Repr. 2, H361d.

Concerning fertility Austria commented that it is unclear whether the death of the dams observed in the 1st study (on days 0, 4 and 11 p.p. in F0 dams and on days 2, 2 and 4 p.p. in F1 dams) but not in the 2nd study (both studies with comparable dose ranges) is due to dystocia. According to the study author, the dams died without obvious cause. There might be a suggestion that the different findings of the 1st and the 2nd study could be attributed to differences in purity of the batches of test material used. Since the current specification for penconazole (> 95%) is intermediate between the two test batches, no statement can be made about the possible influence of impurities. Indeed, according to Regulation (EC) 1272/2008, effects on parturition belong to "adverse effects on sexual function and fertility". However, it is unclear whether the deaths of the dams after parturition were due to dystocia. It should be kept in mind that the observed toxicity in dams given 2000 ppm in the 1st study was limited to reduced body weight gain of -8% and -16% (F0 and F1 dams, respectively) and lower food consumption (-5% and -9% in F0 and F1 dams, respectively), accompanied by increased relative liver weight and hepatocellular hypertrophy. It may be that the reduction in food consumption observed was (as suggested by Austria) not sufficient to fully explain the observed reduction in BW gain. Therefore, there might be some effects which were not observed, but which caused the death of the dams following parturition.

Developmental toxicity was commented by Austria stating that all malformation types (i.e. in rats: umbilical hernia; in rabbits: bilateral microphthalmia, internal hydocephalus and cleft palate) were either seen at incidences greater than in historical control data (HCD) or no comparison to HCD is reported and all these malformations are considered to be rare. Additionally, malformations per se do not depend on maternal toxicity regarding C&L.

RAC assessment and comparison with criteria

Sexual function and fertility

Penconazole administration did cause some effects on parturition and pregnancy outcome that appeared to be associated with the substance. Such findings are of relevance for this endpoint (CLP Regulation, Annex I, Section 3.3.1.3).

In a rat two-generation study (Fritz, 1983), the duration of pregnancy was prolonged and deaths of dams were seen at the time of parturition. In the F0 generation, the number of dams with pregnancy duration of greater than 21 days was 2/20, 4/20, 6/20 and 10/19 at 0, 80, 400 and 2000 ppm; the mean duration of pregnancy was 21.1 days at 0 ppm and 21.6 days (statistically significant) at 2000 ppm. Additionally, one dam of the mid-dose group died during delivery, with further maternal deaths occurring post parturition in the high- (3 dams) dose group. In the F1 generation, the number of dams with pregnancy duration of greater than 21 days was 4/19, 6/18, 2/17 and 14/19 at 0, 80, 400 and 2000 ppm; the mean duration of pregnancy was 21.3 days at 0 ppm and 21.8 days at 2000 ppm. The number of dams that died was in F0 0, 0, 1 (day 0 p.p.), 3 (days 0, 4, 11 p.p.) at 0, 80, 400 and 2000 ppm; additional maternal deaths occurred in F1 in 1 (day 19 p.p.), 0, 1 (day 0 p.p.), and 3 (days 2, 2, 4 p.p.) dams at 0, 80, 400 and 2000 ppm, respectively. Note the study report was not consistent in the pregnancy duration and in the timing and number of the deaths. There was no obvious cause of the deaths and clinical signs prior to the onset of parturition were not reported. Body weight gain of the F0 females was reduced during pregnancy (not dose-related) and in the F1 high-dose females (-16% compared with the controls). The observed effects on reproduction and litter parameters (live litter size and total litter losses) were most likely secondary to the prolonged duration of pregnancy and difficulties with delivery. Effects on pregnancy duration and parturition

did not occur in a second rat (different strain) two-generation study conducted with a slightly higher top dose (Schardein, 1987).

The developmental studies also provided some information on effects on pregnancy / parturition. In one rat study (Fritz, 1981), some maternal toxicity was seen (13 % reduction in body weight gain, slightly reduced food consumption) at the high dose (300 mg/kg/d). In this main study, 2/25 dams in the high-dose group died on GD 21 without other signs of toxicity. In a supplementary study to investigate this unusual finding, 0/15, 4/15 and 2/15 dams at 0, 300 mg/kg/d (dosed GD 6-15) and 450 mg/kg/d (dosed GD 10-14) died on GD 21. However, it should be noted that one of the dams at 300 mg/kg/d that died showed no sign of being pregnant. No pathological findings were noted on necropsy. In all cases, deaths occurred up to 5 days after the end of treatment and about one day before natural parturition should have commenced. No such effects occurred in a second developmental toxicity study in rats (Salamon 1985), where the top dose tested (500 mg/kg/d) was maternally toxic.

Also, in one rabbit study (Nemec, 1985) there was evidence of premature parturition in all treated groups for which a relationship to substance administration could not be excluded. Five treated does delivered 1 day prior to or on the day of the scheduled caesarean section (0/18, 2/16, 2/14, 1/18 at 0, 10, 50, 200 mg/kg/d, respectively, without a clear dose-response relationship). All their foetuses were normal and necropsy findings did not indicate any treatment-related findings. The historical control incidence for premature delivery was reported to be about 3 %, whereas the combined incidence in the penconazole-treated groups in this study was about 10%. Some maternal toxicity was seen in the high dose group (mild clinical signs, body weight loss and reduced food consumption during the first week of treatment). Penconazole did not affect the duration of pregnancy or the onset of parturition in another rabbit developmental study when tested up to 150 mg/kg/d (Giese, 1982).

Total litter loss at birth or in the postnatal period was increased in the F0 mating of a two-generation rat study (Fritz, 1983) only at the high dose, and appeared to be related to the problems with parturition that were experienced by the dams. In the same study, the main impact on the *live litter size* (which was reduced in the high-dose F0 and F1groups) was dead pups at birth which, likewise, was probably a consequence of the prolonged pregnancy and difficulties in parturition. These effects, therefore, should be considered as ones on sexual function and fertility rather than developmental toxicity.

<u>Weight of evidence (WoE) considerations:</u>

Effects on duration of pregnancy and on death of dams were seen in some studies, but not in others. The inconsistency in results was observed between studies, between and within species and within the effects. Death of dams was seen in a rat 2-generation (Fritz, 1983) and developmental study (Fritz, 1981) conducted by one laboratory in one strain of rats, but not in a 2-generation (Schardein, 1987) and developmental study (Salamon, 1985) with other strains of rats at slightly higher doses tested, nor in developmental studies with rabbits (Giese, 1982; Nemec, 1985). In the Fritz 1981 study deaths occurred about 1 day before natural parturition would have commenced. This is an unusual finding and the relevance is unknown. In the Fritz 1983 study a small number of dams died at or shortly after parturition (1 dam each at 400 mg/kg/d in F0 and F1 and at 2000 mg/kg/d in F0), but others (with increased pregnancy duration) died 2 days or later after parturition. The relevance of these later deaths, which also occurred in one control dam, is not clear, but they are probably more related to maternal toxicity than to dystocia. It is further noted that the Fritz 1983 study report was not consistent in the timing and number of the deaths.

As to the duration of pregnancy, a prolonged duration was seen the rat 2-generation study by Fritz

1983 (together with possible consequences for total litter loss and live litter size), but not in the rat 2-generation by Schardein 1987 that was conducted with a slightly higher top dose. In rabbits on the other hand, premature parturition was seen, but only in one study (Nemec, 1985), not in a second study with another strain (Giese, 1982). The relevance of the finding in the Nemec study is doubtful, given the absence of dose-response and all foetusus being normal.

Looking at all data available, the effects on pregnancy duration and on death of dams are difficult to interpret as to the need to classify them, given the inconsistencies observed in the findings and, for the 2-generation study, in the study reporting. The overall WoE consideration is that there is no clear link between the death of dams and dystocia, nor between penconzole treatment and prolonged pregnancy. Therefore no classification for sexual function and fertility according to Regulation (EC) 1272/2008 and Directive 67/548/EEC is warranted.

Developmental toxicity

Several findings that were possibly indicative of developmental toxicity were observed in the available studies. These are summarised and discussed below.

Increased *post-implantation loss* was recorded in two rat developmental studies. In the Fritz (1981) study, the incidences of early resorption were 4.8%. 5.9%, 8.1%, 9.0% at 0, 30, 100, 300 mg/kg/d. None of these increases was statistically significant. The increased post-implantation loss of the high-dose group occurred together with some maternal toxicity (-13% in the corrected weight gain) and this was only just above the historical control mean of 8.9%. At the mid- and low- doses, the incidences of early resorption were increased without evident maternal toxicity but were within the historical control mean. In the Salamon (1985) study, the incidences of resorptions expressed as a % of implantations were 2.2%, 4.4%, 3.6% and 18.9% at 0, 5, 100 and 500 mg/kg/d, respectively. Only the increase at the highest dose was statistically significant; at this dose, however, the maternal toxicity was considerable (death of 2/25 dams, severely reduced body weight gain (-41%), clinical symptoms that included emaciation, weakness and lethargy). At the other doses, a clear dose-related effect was not seen.

Some increases in early resorptions, expressed as a % of implantations, were reported in the rabbit studies. In the Giese (1982) study, these were 4.8%, 6.0%, 0.9% and 9.7% at 0, 20, 75 and 150 mg/kg/d, respectively. At the high dose, maternal toxicity in the form of reduced body weight development was noted at different time points, notably at GD 6-11 (50% reduction). In the Nemec (1985) rabbit study, the incidences of early resorptions were 6.6%, 12.5%, 1.4% and 16.4% at 0, 10, 50 and 200 mg/kg/d, respectively. It should be noted that, in the case of the high-dose group, one of the females was responsible for one third of the cases of resorptions. Maternal toxicity was evident in this group in the form of a 37% reduction in daily food consumption during treatment (GD 7-20, but particularly marked during the first week), which was associated with weight loss over the same time period, such that there was almost no weight change throughout pregnancy. None of the findings in the rabbit studies was statistically significant and clear dose–response relationships were not apparent.

Statistically significant decreases in *pup weight* were recorded in the two multi-generation rat studies (Fritz 1983 and Schardein 1987) at the high dose (up to 16.5%, but mostly less than 10%) at PND 14 and 21, and in the Schardein study also at PND 4 and 7 (F2 only). There was also a decrease in parental body weight and an increase in relative organ weight in pups and parents in these studies.

Incomplete/absent skeletal ossification was recorded in two rat and one rabbit developmental

studies (Fritz, 1981; Salamon, 1985; Nemec, 1985) but only in the presence of maternal toxicity. Such findings are regarded as variations or delays in development. In association with maternal toxicity such effects may not merit classification. Supernumerary cervical ribs, which were reported in one rat study (Salamon, 1985), also in association with maternal toxicity, do not normally lead to classification on their own, since there is no consensus on their relevance to developmental toxicity.

Malformations were also seen in some instances. Microphthalmia and hydrocephalus occurred in one study (Giese 1983) with Chinchilla rabbits at 150 mg/kg/d. One foetus had bilateral microphthalmia alone, giving an incidence (foetal: 0.8%; litter: 6.3%) that was within the historical control range (foetal range 0-4.1%, mean 0.052%; litter range 0-12.5%, mean 1.6%, same strain and laboratory). Two further foetuses had bilateral microphthalmia in combination with internal hydrocephalus, giving incidences of 1.6% (foetal) and 12.5% (litter); these were just outside the historical control range for internal hydrocephalus (foetal range 0–0.9%, mean 0.09%; litter range 0–7.1%, mean 0.7%). The combined incidence of microphthalmia in the three affected foetuses (2.4%) was still within the range of the historical control data. These kinds of rare malformations are unlikely to be related to the maternal toxicity observed (changes in body weight development). In this study, other severe malformations also occurred at the high dose but only as single cases. In another rabbit study but with a different strain (New Zealand White) and at a higher maximum dose (200 mg/kg/d, associated with maternal toxicity), these effects were not seen (Nemec 1985), nor did they occur in two rat developmental studies at doses up to 500 mg/kg/d. In the rat studies (Fritz 1981 and Salamon 1985) there was an increase in the number of foetuses with abnormalities but the effects on the different malformations were not consistent and were generally within the range normally seen for the laboratories; they were therefore regarded by the study authors as spontaneous occurrences.

WoE considerations:

Effects were seen on several variables. Post implementation loss in the form of early resorptions was seen in all developmental studies at the top dose. In one study (Salamon, 1985) the effect was clear and statistically significant, but associated with considerable maternal toxicity. In the other studies the effect was about two fold and neither consistently above historical controls nor statistically significant, and also here slight to more marked maternal toxicity was observed. However, as the effects are consistently seen in all the studies they can not be disregarded as chance findings. Pup weight was decreased postnatally in both rat multigeneration studies at the high dose. Incomplete/absent ossification occurred in two rat and one rabbit studies, and supernumery cervical ribs in one rat study, all in the presence of slight to considerable maternal toxicity. These variations or delays in development may not warrant classification on their own, especially when associated with maternal toxicity, but here they are regarded to add to the WoE. Finally, and most important, severe malformations were seen in one study in rabbits (Giese, 1982): these were three cases of microphtalmia, two in combination with internal hydrocephalus. This effect can not be disregarded. Other severe malformations seen in the rat and rabbit studies were single cases, not consistent and within historical controls, and do thus not contribute to the WoE. Overall there are several effects on development seen and although these may each not all warrant classification on their own, the WoE of all the effects combined makes classification warranted.

Overall, adverse effects on development are seen in the studies. The effects are not pronounced and consistent in the different studies. However, it would be inappropriate to not classify, as there are effects seen in several studies and it has not been shown that these are irrelevant for humans. It should be noted that this is a borderline case for classification. As no evidence from humans is available, classification in Repr. 1A is not possible. The data are not sufficiently conclusive to place the substance in Repr. 1B. Classification for developmental toxicity as Repr. 2 - H361d according

to Regulation (EC) 1272/2008 and Repr. Cat. 3; R63 according to Directive 67/548/EEC is therefore warranted.

In depth analyses by the RAC (if needed - not included in the opinion)

Impact of impurities

The reported reproductive toxicity studies were performed using various purities of penconazole and contained different types of impurities at various concentrations. However, the impact of impurities to the study results was not explicitly proven and therefore their impact was not taken into account when the relevance of the studies was assessed.

Summaries of reproductive toxicity studies:

Fritz 1983 (Rat, Tif:RAIf(SPF)) (Purity 91.7%):Multigeneration study. Guideline: Similar to OECD 416. Doses males F0; 0-5.5-29-149 F1; 0-6.5-31-166, females F0; 0-7.5-40-202 F1; 0-8.5-42.5-227 mg/kg/d

Parental toxicity was slight in both generations at the high dose, i.e., slight reduction in body weight gain (body weight gain -16% food consumption -9%) and increased liver weight with slight hepatocyte hypertrophy and some evidence of slight liver toxicity. At this dose level there was an increased duration of pregnancy or delayed parturition in F0 and F1 dams associated with maternal death and/or litter loss at birth. Also, a decrease in the pregnancy index, decreased pup weight and changes in organ weights were seen.

Schardein 1987 (Rat, COBS CD) (Purity 98.7%) Multigeneration study. Guideline: OECD 416. Doses males F0; 0-1.95-1935-191 F1; 0-2.2-21.8-219, females (highest) F0; 0-3.32-33.7-346 F1; 0-3.21-32.7-337 mg/kg/d.

Maternal toxicity was seen as body weight gain -9% food consumption -8%. At the high dose there were changes in organ weight and decreased pup weight.

Fritz 1981 (Rat, Tif:RAIf(SPF)) (Purity 88%):Developmental toxicity study. Guideline: Similar to OECD 414. Doses 0-30-100-300 (0-300-450 in supplementary study) mg/kg/d.

At the high dose, moderate maternal toxicity was seen (13 % reduction in weight gain, reduced food consumption (4% less than control). 2/25 dams died on GD 21 without other signs of toxicity. In a supplementary study to investigate this unusual finding, 4/15 dams died on GD 21 at 300 mg/kg bw/day (dosed on GD 6-15) and 2/15 died on GD 21 at 450 mg/kg bw (dosed GD 10-14). No pathological findings were noted on necropsy. It should be noted that in all cases, deaths occurred up to 130 hours after treatment had ended**.** An increase in resorptions was seen and slight effects on ossification and sternum.

Salamon 1985 (Rat, Crl:CD(SD)) (Purity 98.7%) Developmental toxicity study. Guideline: OECD 414. Doses 0-5-100-500 mg/kg/d

Pronounced maternal toxicity was seen. Body weight gain (corrected) -30 % (day 6-21: 41 %), food consumption up to -42%. Embryofoetal toxicity (prenatal lethality, reduced foetal body weights, slight increase in the occurrence of malformed ribs (cervical, 14 pairs)), were present at 500 mg/kg bw/d. An increase in resorptions was seen and slight effects on ossification. Decreased number of live foetuses was also seen.

Giese 1982 (Rabbit, Chinchilla) (Purity 91.7%) Developmental toxicity study. Guideline: OECD 414. Doses 0-25-75-150 mg/kg/d

Reduced maternal body weight gain and reduced food consumption were noted during treatment at 150 mg/kg bw/d (Body weight gain (corrected) +24% food consumption -6%). At this dose there was an increased incidence of bilateral microphthalmia (with or without internal hydrocephalus). The hydrocephalus observed exceeded the historical control incidence; for the microphtalmia, two sets of historical controls were available. The incidence in the study exceeded one but not the other.

Nemec 1985 (Rabbit, NZW) (Purity 98.7%) Developmental toxicity study. Guideline: OECD 414. Doses 0-10-50-200 mg/kg/d

200 mg/kg resulted in maternal toxicity (lower body weight gain and reduced food consumption up to ~day 20, decreased defecation and urination, however, corrected body weight was slightly higher in high dose animals as compared to controls). Five treated does delivered 1 day prior to or on the day of the scheduled caesarean section (0, 2, 2, 1 out of 20 does at 0, 10, 50, 200 mg/kg/d, respectively). All their foetuses were normal and necropsy findings did not indicate any treatment-related condition in the foetuses. The historical control incidence for premature delivery is reported to be about 3 %, whereas the combined incidence in the penconazole-treated groups in this study was about 10. There was evidence of premature parturition in all treated groups for which a relation to substance administration cannot be excluded. There was an increase in resorptions and slight effects on ossification.

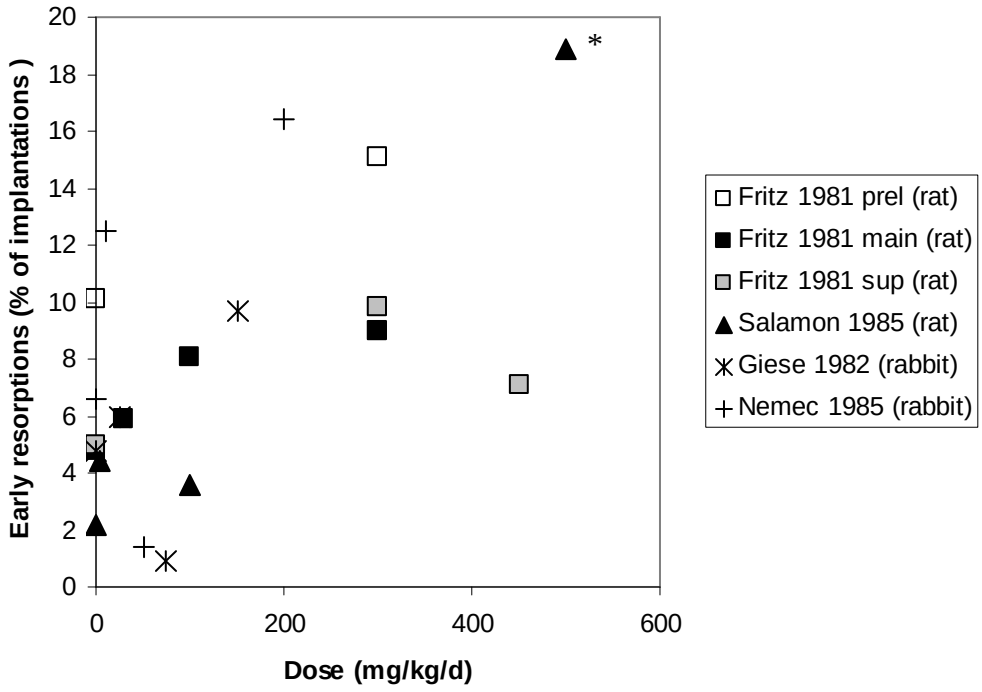
Additional data from the studies discussed in the original proposal

Table 1 Deaths of dams occurring around parturition in Fritz 1983

	0 ppm	80 ppm	400 ppm	2000 ppm
F0	0	0	1 (no.96; PD 21), at parturition	3 (nos 156*; PD 23, 126*; PD 23, 152; PD22), shortly after, 4 and 11 days after parturition, resp.
F1	1 (no.206; PD 25), at 19 days after parturition	0	1 (no.412; PD 21), at parturition	3 (nos 524; PD 23, 536; PD 23, 516; PD 25), at 2, 2, 4 days after parturition, resp.

Deaths of dams and time of death in Fritz 1983. Dose in ppm. No of the dam indicated. PD refers to pregnancy duration. * For these dams the main report and the supplement gave different information on whether the dams had died or not.

Figure 1 Early resorptions



Early resorptions as a function of dose of penconazole. For Fritz 1981 data from the preliminary study (prel) and the supplementary study (sup) were included as well as the main study (main). Species are stated in the legends, for further information on the studies see above. * High maternal toxicity.

Table 2 Pup weight in the multigeneration studies

	F0				F1			
	Fritz 1983		Shardein 1987		Fritz1983		Shardein1987	
	Control	2000 ppm	Control m/f	2500 ppm m/f	Control	2000 ppm	Control m/f	2500 ppm m/f
PND 0			6.2/6.0	6.4/ 6.1			6.5/ 6.1	6.6/ 6.3
PND 4	7.9	7.8	9.5/9.1	9.4/ 9.0	8.7	8.8	10.6/ 9.9	10.1/ 9.6*
PND 7	11.6	11.2	14.9/ 14.4	14.6/14.0	12.8	12.7	17.2/ 16.4	15.3*/14.6*

PND 14	25.8	22.3*	30.2/ 29.5	28.5*/ 27.6*	26.6	24.3	34.2/ 33.0	30.0*/2 9.0*
PND 21	40.6	33.9*	49.8/ 48.3	46.9/ 45.0*	41.2	39.1	55.5/ 52.8	49.6*/4 8.8

* Statistically significant p<0.05

Pup weight are shown for the two multigeneration studies in rats. Only control and high dose shown, no effect was seen at lower doses. For further information on the studies see above.

Table 3 Effects on reproductive organs seen in Schardein 1987:

Table B.6.6-21: Two-generation rat (2nd study) - adult terminal sacrifice: macroscopic and microscopic findings (selection)

Dose level (ppm)				Generation	0	25	250	2500
Macroscopic	Kidney	Hydronephrosis		F_0	-	-	-	1F
				F_1	1M	2M	-	-
	Testes	Small (uni- or bilateral)		F_0	-	-	1	1
				F_1	-	-	3	2
Microscopic	Epididymis: aspermia	No grade		F_0	-	-	-	1
				F_1	-	-	3	2
		Relative	Mild	F_0	-	-	-	1
				F_1	1	-	-	-
			Moderate	F_0	-	1	1	1
				F_1	-	-	-	1
			Severe	F_0	-	-	1	1
				F_1	-	-	-	-
	Testis: tubular atrophy, aspermatogenesis	Mild		F_0	-	-	-	-
				F_1	2	-	-	1
		Moderate		F_0	-	-	1	-
				F_1	-	-	-	-
		Severe		F_0	-	-	-	1
				F_1	-	-	3	1

(Number of parental animals per group: 30M + 30 F)

Effects seen in reproductive organ in rats. Some trend towards more severe effects can be seen with increasing dose but the cases are few and similar effects were not seen in Fritz 1983.

Table 4 Abnormalities findings in Giese 1982

Table B.6.6-41: Prenatal toxicity rabbit (1st study) – overview of foetal findings and abnormalities

Dose level (mg/kg bw/d)	0	25	75	150
Number of foetuses/litters examined	113/16	104/15	102/15	125/16
External findings				
Total foetuses/litters affected	2/2	1/1	0	2/2
% foetuses/litters affected	2/13	1/7	0	2/13
Omphalocele	1/1	0	0	0
Omphalocele and mandibular hypoplasia	0	1/1	0	0
Arthrogryposis of forelimbs	1/1	0	0	1/1
Right forelimbs with 1st and 5th digit missing, cleft lip (unilateral) and cleft palate	0	0	0	1/1
Visceral findings				
Total foetuses/litters affected	1/1	0	0	4/2
% foetuses/litters affected	1/6	0	0	3/13
Agenesis of kidney and ureter	1/1	0	0	0
Hypoplasia of kidneys	0	0	0	1/1
Microphthalmia (bilateral)	0	0	0	1/1
Microphthalmia (bilateral) and internal hydrocephalus	0	0	0	1/1 (2/2 ?)$
Skeletal findings				
Total foetuses/litters affected	4/3	2/2	3/3	3/3
% foetuses/litters affected	4/19	2/13	3/20	3/19
Irregular/asymmetrical ossification of single sternebrae	3/2	1/1	1/1	1/1
Irregular ossification of sternum	0	1/1	0	1/1
Brachymelia and sternum poorly ossified	0	0	0	1/1
Sternebrae nos. 4 + 5 partially fused/irregularly ossified	1/1	0	1/1	0
Sternebrae nos. 4 + 5 partially fused and irregulary ossification of no. 6	0	0	1/1	0

$ according to 2nd study report amendment

Abnormalities found in Giese 1982. There are several severe malformations but apart from microphtalmia with or without hydrocephalus no severe malformation occurs more than once.

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 / development)	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 ≥ 25%	N; R50-53

2.5% ≤ C < 25% N; R51-53

0.25% ≤ 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.

RAC evaluation of environmental hazards

Summary of Dossier submitter's proposal

The dossier submitter proposed classification and labelling for environmental hazards as Aquatic Acute 1 and Aquatic Chronic 1 with an M-factor 1.

Degradability

According to the OECD Guideline No. 301B, Penconazole was not found to be readily biodegradable, because no degradation occurred during 28 days whereas >70% degradation within 28 days is required to achieve this criterion.

In water/sediment systems Penconazole is dissipated primarily by partitioning to the sediment with single first order DT50 of 1.9-3.4 days where it subsequently degraded (whole system pseudo first order DT50 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. In aerobic laboratory soil degradation studies the overall geometric mean DT50 value of Penconazole was 117 days (SFO, 20 °C, pF2). In field soil dissipation studies DT50 values of Penconazole were in the between 67 d – 115 days (SFO). In the field, Penconazole can exhibit slow primary degradation but not ultimate mineralisation. As a result of the field and laboratory studies, Penconazole is considered as not rapidly degradable.

Bioaccumulation

Penconazole has a log Kow of 3.72. The only available experimental bioaccumulation study was performed according to EPA guideline No. 165-4 and the calculated BCFs were based on total radioactive residue. The maximum BCF of 320 for whole fish is considered more reliable estimate than the steady state BCF of 200. Both BCF values are above the Directive 67/548/EEC limit values of 100 but lower than the Regulation (EC) 1272/2008 limit value of 500. Penconazole is thus considered as bioaccumulative according to Directive 67/548/EEC, but not bioaccumulative according to Regulation (EC) 1272/2008.

Ecotoxicity

In fish, LC50s ranged from 1.13 to 3.8 mg/L. A chronic NOEC in fathead minnow *Pimephales promelas* was 0.32 mg/L (Surprenant, 1984; 30 days post-hatch test / internal protocol, based on measured concentrations).

In the water flea *Daphnia magna* EC50 was 6.75 mg/L. In this species NOEC was 0.069 mg/L (Surprenant D.C., 1984; 21-day flow through test, according to an internal method similar to US EPA (1975) Series 660/3-75-009). This NOEC was based on measured concentrations and does not need any correction for the 87.3% purity.

In the algae *Pseudokirchneriella subcapitata* ErC50 (72h) was 4.9 mg/L, but in the duckweed *Lemna gibba* the 14-day EC50 value was 0.22 mg/L (NOEC = 0.087 mg/L) (Hughes, 1985, static 14-day test according to the US EPA proposed Guidelines for Registering Pesticides). In this study, the substance purity was 87.3%, so the toxicological values were corrected to 100% active ingredient nominal concentrations.

Comments received during public consultation

Several member states (Belgium, the Netherlands, France, the UK, Sweden) commented proposed environmental hazard classification and labelling of penconazole. All comments agreed with the proposed classification and labelling.

Most of the comments concerned editorial issues or data reporting. Some comments brought up the appropriateness of 7- and 14-days *Lemna* studies for the purpose of determining an EC50 and NOEC and further consideration of the results of 7-day was recommended.

Lack of analytical verification of test concentrations in some studies was commented and the low purity of the test material was recommended to be taken into account when defining threshold values (corrected values are available in the revised report in Annex 2).

Some comments concerned data that does not have relevance for classification and labelling and was recommended to be removed. Also, it was brought up that degradation and bioaccumulation have separate criteria and should be assessed independently.

RAC assessment and comparison with criteria

According to Regulation (EC) 1272/2008:

As the acute toxicity of Penconazole in *Lemna gibba* (14-day EC50 = 0.19 mg/L) is above 0.1 mg/L but below or equal to 1 mg/L, classification as aquatic acute category 1 – H400 and an M-factor of 1 are required.

The chronic toxicity of Penconazole in *Daphnia magna* (0.01 mg/L < water flea flow-through 21-day test NOEC = 0.069 mg/L ≤ 0.1 mg/L) is above 0.01 mg/L but below or equal to 0.1 mg/L. Since Penconazole does not meet the criteria of rapid degradation, classification as aquatic chronic category 1 – H410 and an M-factor of 1 are required.

According to Directive 67/548/EEC:

The acute toxicity of Penconazole in *Lemna gibba* (14-day EC50 = 0.19 mg/L) is below or equal to 1 mg/L and Penconazole does not meet the criteria of ready biodegradability in the OECD-301B test. Classification as N; R50/53 with the specific concentration limits as given below are required.

N; R50/53: C ≥ 25%
N; R51/53: 2.5% ≤ C < 25%
R52/53: 0.25% ≤ C < 2.5%

In addition to the data presented in the CLH report, RAC is aware that Penconazole, like other ergosterol biosynthesis inhibiting (EBI) substances, is under particular regulatory scrutiny with regard to their potential for endocrine disruption. For these substances, e.g. the (re-)approval process may generate further data from long-term fish studies like full life-cycle or sexual development tests, if requested for the underlying risk assessment.

Based on the provided data in the CLH report, RAC agrees with the dossier submitter's proposal to classify Penconazole for **Aquatic acute 1 and Aquatic chronic 1 according to CLP and N; R50/53 according to DSD** (with the specific concentration limits as given above). However, seperate M-factors, i.e. Acute M-factor 1 and Chronic M-factor 1, are warranted according to the 2nd ATP of CLP.

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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