Annex VI Report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Fuberidazole

EC Number: 223-404-0

CAS Number: 3878-19-1

Submitted by: UK REACH Competent Authority

Author: Chemicals Regulation Directorate,
Health and Safety Executive,
United Kingdom.

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BACKGROUND

Fuberidazole is a benzimidazole fungicide that is used as a seed treatment. In 2008 it was approved for Annex I listing as a 3A Review compound under Council Directive 91/414/EEC, with the UK as Rapporteur Member State. In accordance with Article 36(2) of the CLP Regulation, fuberidazole should now be considered for harmonised classification and labelling. Therefore, this proposal considers all human health and environmental end points. This Annex VI dossier presents a classification and labelling proposal based mainly on the information presented in the assessment of fuberidazole under Directive 91/414/EEC. The assessment made under that Directive is attached to the IUCLID 5 dossier.

Fuberidazole is listed on Annex VI of the CLP Regulation (it was inserted into Annex I of Directive 67/548/EEC in the 19th ATP in 1993) with the classifications of Xn; R22 and N; R50-53. This proposal seeks to confirm these classifications and additionally, based on the evaluation of some existing and some new data, to include classifications for skin sensitisation and repeated dose toxicity.

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance name: Fuberidazole

EC number: 223-404-0

CAS number: 3878-19-1

Registration number(s):

Purity: The minimum purity is 97%

Impurities: The manufacturer has requested that all impurities remain confidential. Some impurities have been identified to be present in batches generated for toxicological studies at concentrations up to 1.5%. However, according to the present specification of industrially-produced fuberidazole technical material, all impurities are individually present at ≤ 0.4%. The European Commission has declared that, on the basis of information available at the time of the review under Directive 41/414/EEC, none of the impurities are of toxicological or environmental concern (EC SANCO 3620/07, 20 May 2008).

Proposed classification based on Directive 67/548/EEC:

Xn; R22 (already included in Annex I of Regulation EC/1272/2008)
Xi; R43
Xn; R48/22
N; R50-53 (already included in Annex I of Regulation EC/1272/2008)

Proposed classification based on CLP criteria:

Acute toxicity category 4; H302
Skin sensitisation category 1; H317
STOT RE 2 (heart); H373
Aquatic Acute 1; H400: very toxic to aquatic life
Aquatic Chronic 1; H410: very toxic to aquatic life with long lasting effects

Proposed labelling based on Directive 67/548/EEC:

Class of danger:	Harmful; irritant
R phrases:	22-43-48/22-50/53
S phrases:	(2)-24-37-60-61

Proposed labelling based on CLP Regulation:

Pictogram:	GHS07, GHS08, GHS09
Signal word:	Warning

Hazard statement codes: H302, H317, H373, H400, H410
Precautionary statements: Not required as PS are not included in Annex VI

Proposed specific concentration limits (if any):

Classification of the preparation		
N, R50-53	N, R51-53	R52-53
Cn ≥ 25 %	2.5 % ≤ Cn <25 %	0.25 % ≤ Cn <2.5 %

Where Cn is the concentration of fuberidazole in the preparation.

Under CLP M factor 1 based on 0.1 <L(E)C_{50} ≤1 mg/l.

Proposed notes (if any):

None

JUSTIFICATION

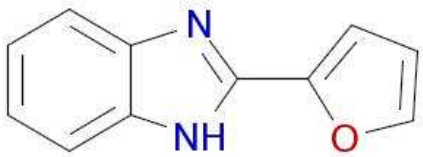
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name: Fuberidazole
EC Number: 223-404-0
CAS Number: 3878-19-1
IUPAC Name: 2-(2-furyl)-1H-benzimidazole

1.2 Composition of the substance

Chemical Name: Fuberidazole
EC Number: 223-404-0
CAS Number: 3878-19-1
IUPAC Name: 2-(2-furyl)-1H-benzimidazole
Molecular Formula: $C_{11}H_8N_2O$
Structural Formula:



Molecular Weight: 184.2
Typical concentration (% w/w) > 97% (no individual impurities present at > 0.4% in the material being placed on the market)
Concentration range (% w/w) Not available

1.3 Physico-Chemical properties

The physico-chemical properties of fuberidazole have been well investigated, as summarised in the Pesticide Assessment Report attached to the IUCLID 5 dossier. Some of the key information is provided in the table below. In all the studies below the purity of the test substance was ≥ 96.9%. No classification is justified.

Table 1. Summary of physico-chemical properties

REACH ref Annex, §	**Property**	**Value**	**Reference**
VII, 7.1	Physical state at 20 C and 101.3 KPa	Colourless crystalline solid	Reference 1
VII, 7.2	Melting / freezing point	285-301 C	EU A1 Reference 1
VII, 7.3	Boiling point	In DTA an exothermic reaction at 390ºC was observed	OECD 113 Reference 1
VII, 7.4	Relative density	1.25	Reference 1
VII, 7.5	Vapour pressure	$9x10^{-7}$ Pa at 20 C (extrapolated) $2x10^{-6}$ Pa at 25 C (extrapolated)	OECD 104 Reference 1
VII, 7.6	Surface tension	72.35 mN/m at 20 C	OECD 115 Reference 1
VII, 7.7	Water solubility	71 mg/L at 20ºC and pH 7	OECD 105 Reference 1
VII, 7.8	Partition coefficient n-octanol/water (log value)	2.78 at pH 7 and 20ºC	OECD 107 Reference 1
VII, 7.9	Flash point	N/A (fuberidazole is a solid)	
VII, 7.10	Flammability	Not highly flammable and does not liberate gases in hazardous amounts in contact with water	EU A10 & A12 Reference 1
VII, 7.11	Explosive properties	Not sensitive to heat, shock or friction	EU A14 Reference 1
VII, 7.12	Self-ignition temperature	Does not spontaneously combust	EU A16 Reference 1
VII, 7.13	Oxidising properties	Not oxidising	EU A17 Reference 1
IX, 7.16	Dissociation constant	pKa approx. 4	OECD 112 Reference 1

2 MANUFACTURE AND USES

Fuberidazole is manufactured and placed on the market for application as a fungicidal seed treatment.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex VI of the CLP Regulation

Fuberidazole (index number 613-016-00-3) was classified in the 19th ATP (1993) of Directive 67/548/EEC as Xn; R22, N; R50-53.

3.2 Self classification(s)

The classification in Annex I of Directive 67/548/EEC (now Annex VI of the CLP Regulation) is that which is applied by industry.

4 ENVIRONMENTAL FATE PROPERTIES

4.1 Degradation

4.1.1 Stability

Hydrolysis
The results of a hydrolysis study (Reference 9) following US EPA guidelines (161-1) using phenyl-*UL*-^{14}C radiolabelled fuberidazole showed it is hydrolytically stable under acidic (pH 5), neutral (pH 7) and alkaline (pH 9) conditions. The test was run at pH 4, 7 and 9 at 50^{o}C over seven days in the dark. At termination, greater than 90 % of Applied Radioactivity (AR) was associated with the parent substance and only minor degradants were detected. The DT_{50} values at 50^{o}C were as follows; 126 days at pH 4; 1,694 days at pH 7; and, 307 days at pH 9. Given the limited hydrolysis at 50^{o}C, additional testing at 25^{o}C was not undertaken and fuberidazole is considered hydrolytically stable under environmentally relevant pH and temperature conditions.

Aqueous photolysis
An aqueous photolysis study (Reference 9) following US EPA guidelines (161-2) using a phenyl-*UL*-^{14}C radio label showed that fuberidazole undergoes photodegradation. The study involved subjecting buffered sterile pure water samples at pH 7 and 25^{o}C, with 0.5 mg/l test substance to continuous irradiation which was calculated to be the equivalent to 0.72 solar days or a 24 hour period in June at 34^{o}N.
The experimental half-life was 1.03 experimental hours. Considering first order direct photodegradation, this equates to an estimated DT_{50} of 0.15 solar days (3.6 hours), ~40 degrees latitude (southern Europe) under midsummer sun.

Three major degradation products were identified; 2-carboxybenzimidazole (M01); cis-oxobutenoic acid (M16); and trans-oxobutenoic acid (M17). Based on Applied Radiation (AR), these were formed at a maximum of 11.1 % AR (at 5 hours), 46.3 % AR (at 4 hours) and 22.1 % AR (at 4 hours) respectively. First order DT_{50} values under midsummer sun at ~40 degrees latitude, in the top layer of pure water were calculated as; 12.7, 1.44, and 0.72 hours for each degradation product respectively.

The quantum yield and phototransformation of fuberidazole in water was evaluated following UBA guidelines (Reference 9). The method assessed the number of degraded molecules and light absorbance by the substance to determine the substance quantum yield. This is used to determine environmental half-lives. In the study, two models were applied to estimate environmental half-lives in waters.

The first using the GC-SOLAR simulation model, estimated half-lives based on the 10th degree longitude, top 0-1 cm of a pure water column, under clear skies. At the 50th degree latitude (central Europe) the environmental half-life ranged between 0.3 days in summer to 4 days in winter. At the 60th degree latitude (Scandanavia) the environmental half-life ranged from 0.4 days in summer to 19 days in winter.

The second using the Frank and Klöpffer simulation model, estimated the following half-lives for the top 0-1 cm of a pure water column at 50th degree latitude (central Europe) with typical cloudiness; 1.2-9.4 days in March; and, 1.8-15 days in October.

These studies show fuberidazole is susceptible to direct photodegradation.

The stability in air is not considered relevant for this type of dossier given that air is not considered an environmental compartment of concern for fuberidazole (see Section 4.2.2).

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

A QSAR estimate using EPIWIN v.3.11 (Reference 12) gives Biowin 2 = 0.597, Biowin 3 = 2.7921 and Biowin 6 = 0.1245. This means that the substance is anticipated to have the following half-lives; < 60 days in marine water; < 40 days in freshwater or estuarine water; < 180 days in marine sediment; and, < 120 days in freshwater or estuarine water sediment. This indicates that fuberidazole does not meet the REACH Screening criteria (Reference 13) for persistence[1]. It should be noted that is unclear if the substance meets the domain of the QSAR model.

4.1.2.2 Sreening tests

A ready biodegradation study is not available.

4.1.2.3 Simulation tests

Following OECD (308), SETAC and EPA (162-4) guidelines, aerobic water/sediment degradation of fuberidazole was assessed (Reference 9) using water/sediment from the Anglersee and Hönniger Weiher water bodies in Germany. The study using phenyl-*UL*-^{14}C radiolabelled fuberidazole involved incubating test flasks without plants over 100 days in the dark at 20 ±1 ^{o}C.

Anglersee
The water pH was 6.9-8.1 and sediment pH was 6.6. The sediment phase comprised 4.9 % clay, 17 % silt, and 78.1 % sand. The organic carbon content was 1.1 %. Aquatic fuberidazole concentrations decreased and by day 14 it was not detected in water based on Applied Radioactivity (AR) measurement. This decrease coincided with an increase in fuberidazole concentrations in sediment which appeared to peak around day 3 at 58.1 % AR. By day 31, 22.9 % fuberidazole was present in sediment. At this time, CO_2 evolution accounted for 6.6 % AR with the remaining AR principally attributed to unextracted sediment residues (47.8 % AR) and degradants M01 (7 % AR) and M11 (3.2 % AR). Fuberidazole DT_{50} values based on first order kinetics (non linear regression) were as follows; 0.83 days for water; 21.7 days for sediment; and 12.4 days for the entire system.

Hönniger Weiher
The water pH was 5.8-7.2 and the sediment pH was 5.0. The sediment phase comprised 12.9 % clay, 40.7 % silt, and 46.4 % sand. The organic carbon content was 3.7 %. Aquatic fuberidazole concentrations decreased and by day 14 it was not detected in the aqueous phase based on Applied Radioactivity (AR) measurement. This decrease coincided with an increase in fuberidazole concentrations in sediment which appeared to peak around day 3 at 64 % AR. By day 30, 26 % fuberidazole was present in sediment. At this time, CO_2 evolution accounted for 2.4 % AR with the remaining AR principally attributed to unextracted sediment residues (49.9 % AR) and degradants M01 (2.5 % AR) and M11 (2.8 % AR). Fuberidazole DT_{50} values based on first order kinetics (non

[1] If Biowin 2 <0.5 (does not biodegrade fast) and Biowin 3 <2.2 (ultimate biodegradation timeframe ≥ months) then substance considered persistent. If Biowin 6 <0.5 (does not biodegrade fast) and Biowin 3 <2.2 (ultimate biodegradation timeframe ≥ months) then substance considered persistent.

linear regression) were as follows; 0.34 days for water; 31.5 days for sediment; and 17.8 days for the entire system.

In both the Anglersee and Hönniger Weiher systems the decrease in concentration of AR in the aquatic phase mirrored the increase in concentration of AR in the sediment phase. On this basis, the water DT_{50} is considered to represent partitioning to sediment. The slightly shorter water DT_{50} value for the Hönniger Weiher system may reflect the slightly higher organic carbon content and lower sand proportion.

The study indicates that fuberidazole partitions to sediment fairly rapidly where it undergoes transformation. No degradation products were observed in water. Two degradation products were identified in sediment; 2-carboxybenzimidazole (M01) and acetylbenzimidazole (M11). At day 30 these comprised 2.5 and 2.8 % AR respectively. Further modelling (Reference 9) indicates first order kinetics (non linear regression) DT_{50} values for M01 as follows: 41.1 days for the Anglersee entire system, and 78.1 days for the Hönniger Weiher entire system.

Overall, the study demonstrates that fuberidazole dissipates from water by rapid partitioning to sediment where it undergoes degradation over a longer period of time.

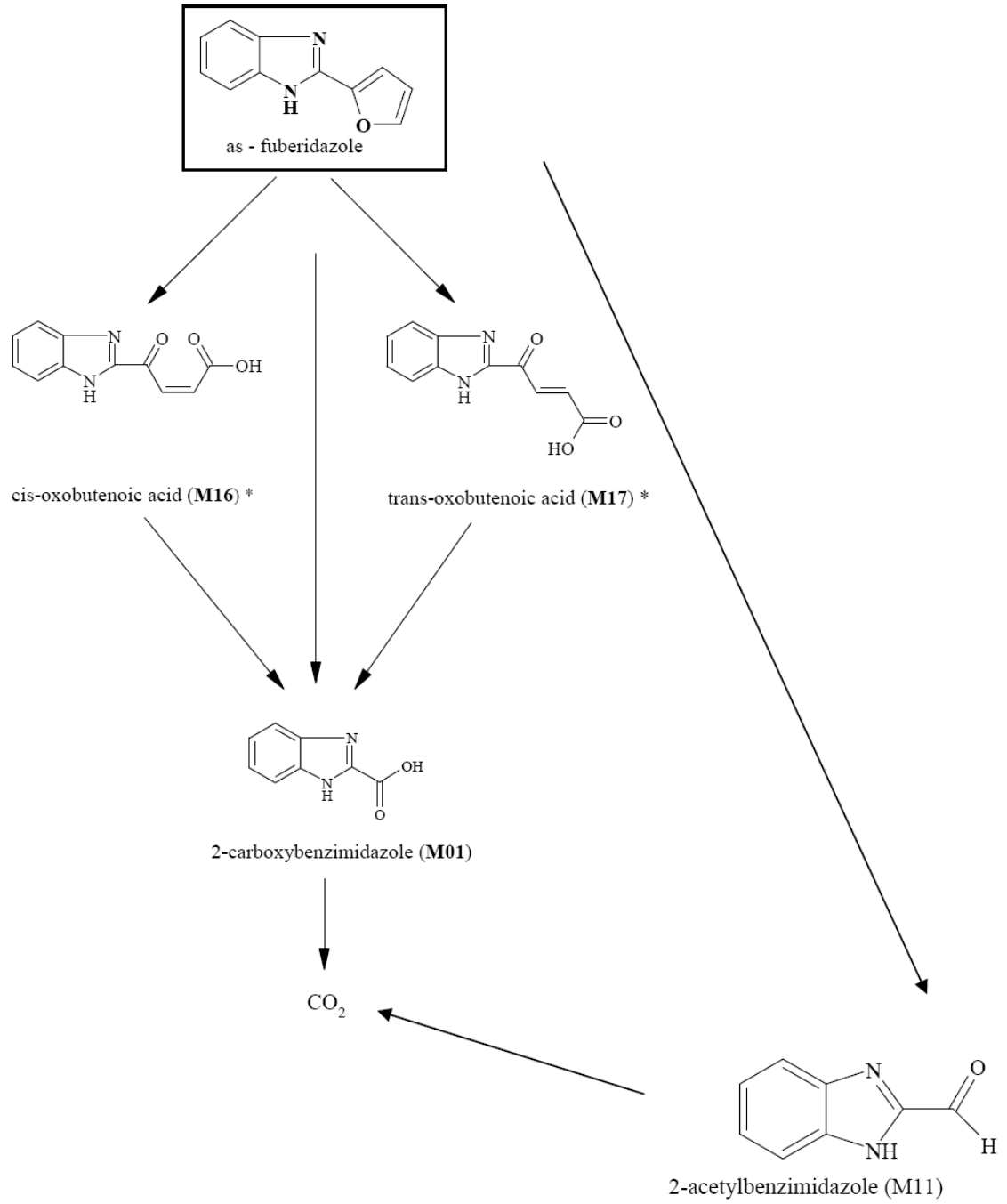
4.1.3 Summary and discussion of persistence

A proposed degradation pathway for fuberidazole is presented in figure 1.

Fuberidazole is considered hydrolytically stable under environmentally relevant pH and temperature conditions. It is susceptible to photodegradation in the environment. However, fuberidazole rapidly dissipates from water by rapid partitioning to sediment where it has a longer residence time. Under environmentally relevant conditions, where suspended solids are likely and light penetration limited (especially at different times of the year in different EU locations), significant environmental photodegradation of fuberidazole is considered unlikely to occur before partitioning to sediment.

Once partitioned to the sediment phase, photodegradation is unlikely to be an important degradation pathway. Considering this and levels of mineralisation in the simulation study, fuberidazole is not considered to undergo rapid and ultimate degradation under environmental conditions and is considered not readily degradable (<70 % mineralisation in the aquatic environment within 28 days) for the purpose of classification and labelling.

Figure 1 - A proposed degradation pathway for fuberidazole (based on photodegradation and water/sediment simulation studies).



*breakdown products only identified in laboratory aqueous photolysis studies.

4.2 Environmental distribution

4.2.1 Adsorption / desorption

Two studies following OECD (106) and US EPA (163-1) guidelines are available. Each determined adsorption constants using ^{14}C radiolabelled fuberidazole and various soils. The first study (Reference 9) employed three soils, ranging from sand to loamy sand, (pH 5.6, 5.8, 5.4). The K_{oc}

adsorption constant range was 645-698 ml/g. The second study (Reference 9) employed one silt soil (pH7.6). The K_{oc} adsorption constant was 420 ml/g and the K_{oc} desorption constant was 677 ml/g.

A further adsorption/desorption study (Reference 9) is available for the degradant M01 (2-carboxybenzimidazole). The test followed OECD (106) and US EPA (163-1) guidelines and used three soils ranging from sandy loam to silt. The K_{oc} adsorption constant range was 257-308ml/g. The K_{oc} desorption constant range was 454-513 ml/g.

Although fuberidazole is a weak base, considering the two studies there appears to be no trend for lower pH soils to have lower adsorption values.

These studies indicate fuberidazole is reasonably strongly absorbed to all tested soils while the degradant M01 is moderately mobile in soil.

4.2.2 Volatilisation

Fuberidazole has a low extrapolated vapour pressure of 2×10^{-6} Pa at 25 °C (Reference 1) and a low Henry's Law Constant (2×10^{-6} Pa × m^3× mol^{-1} at 20 °C) (Reference 1) based on measured data. On this basis fuberidazole is considered unlikely to partition to air.

4.2.3 Distribution modelling

Not relevant to this type of dossier

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

Following OECD Guideline 107, at 20°C fuberidazole has measured log K_{ow} values of 0.78-2.51 at pH 2.8-5.0, 2.78 at pH 7, and 2.79 at pH 9 (Reference 1). The logK_{ow} increases with increasing pH but all values are below 3 indicating a low bioaccumulation potential. On this basis a fish aquatic bioaccumulation study has not been conducted.

For example, a BCF_{fish} of 46.9 $l/kg_{wetfish}$ can be estimated based on the highest log K_{ow} measurement, following Equation 74 in the Technical Guidance Document (2003) (Reference 11). This log K_{ow} value is within the domain of the QSAR (log K_{ow} 2-6).

Fuberidazole was observed to be extensively metabolised in metabolism studies using rats (Reference 2) (refer to section 5.1). Although a slower rate of metabolism could be expected to occur in fish, it is assumed that fuberidazole is unlikely to bioaccumulate in fish.

4.3.1.2 Measured bioaccumulation data

No experimental data are available.

4.3.2 Terrestrial bioaccumulation

Not relevant for this type of dossier.

4.3.3 Summary and discussion of bioaccumulation

Based on the measured log K_{ow} values (<3) and estimated BCF_{fish} (46.9) fuberidazole is considered to have a low bioaccumulation potential.

4.4 Secondary poisoning

Not relevant for this type of dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

Fuberidazole manufactured for use as a pesticide has a minimum purity of 97%. The fuberidazole used in the following studies had a purity that was typically ≥ 96.1%, unless stated otherwise. After careful and detailed review by the UK CA and those authorities responsible for the assessment under Directive 91/414/EEC, these studies have been judged to be adequate for the substance that is being marketed.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

The following summary is derived from the assessment made for the review under Directive 91/414/EEC.

All the following toxicokinetic information on fuberidazole was acquired from rat studies. Fuberidazole was well absorbed (≥ 80%) following single and repeat oral dosing; repeat dosing appeared to result in more rapid absorption than single dosing. Dermal absorption in the rat was ≤ 10%. There is no available information on the absorption of fuberidazole by the inhalation route. Distribution after oral absorption was widespread, with the highest concentration being in the liver and kidney, and, from 24 hours after dosing, additionally the nasal mucosa and thyroid. The substance was extensively metabolised in rats with a broadly similar pattern in males and females. The main metabolic pathway was hydroxylation followed by conjugation and/or internal cleavage of the furan ring and oxidation of the side chain. Elimination from the body was rapid (80-90% in 24 hours) and occurred via the urine and faeces (in similar proportions). Only 0.3 to 1.4% of the excreted dose was in the form of the parent compound. The proportion of eliminated dose in expired air accounted for less than 1% of the administered dose. The available information did not indicate that bioaccumulation of fuberidazole or its metabolites occurred (Reference 2).

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Table 2.1. Acute oral toxicity

Species/Dose	LD_{50}	Observations and remarks
Rat/Wistar, 3 females/group 200, 500, 2000 mg/kg OECD 423 (‘acute toxic class’) GLP (Krötlinger, 2003a in Reference 2).	Between 300 and 500 mg/kg	Deaths occurred from days 2 to 9. Clinical signs included piloerection, constipation, decreased motility and reactivity, uncoordinated gait, laboured breathing, narrowed palpebral fissures, yellow discoloured chippings, closed eyelids, dazed condition and poor reflexes. Gross necropsy of those animals that died during the study revealed autolysis; pale and spotted discoloration of the liver; slightly collapsed lung; and pale discoloration of the kidneys.

Rat (strain unspecified) 10 females/dose 500, 750, 1000 mg/kg Not guideline or GLP (Thyssen, 1974 in Reference 2).	792 mg/kg	There was no information on when the deaths occurred, clinical signs or changes at gross necropsy.
Rat (strain unspecified) 10 females/dose 150, 250, 350, 500, 750, 1000, 1500, 2000 mg/kg Not guideline or GLP (Mihail, 1981 in Reference 2)	477 mg/kg	There was no information on when the deaths occurred, clinical signs or changes at gross necropsy.

5.2.2 Acute toxicity: inhalation

Table 2.2. Acute inhalation toxicity

Species/Dose	LC_{50}	Observations and remarks
Rats/Wistar 5/sex 0, 0.458 mg/L for 4 hours OECD 403 (nose-only) GLP (Pauluhn, 2003 in Reference 2)	> 0.458 mg/L	The starting material was a crystalline solid. 0.458 mg/L was the maximum attainable concentration. The mass median aerodynamic diameter (MMAD) of the aerosol particles was 8.72 µm. This relatively high MMAD value was an unavoidable consequence of the equipment that was necessary to achieve the maximum possible dust concentration. No deaths occurred. Clinical signs of toxicity were indicative of respiratory distress together with some non-specific findings: piloerection, hair-coat ungroomed, bradypnoea, laboured breathing, tremor, reduced motility, serous nasal discharge, red encrustations of nostrils, decreased body weights and hypothermia. Findings at necropsy included collapsed lungs and some white discoloration of the lungs.

5.2.3 Acute toxicity: dermal

Table 2.3. Acute dermal toxicity

Species/Dose	LD_{50}	Observations and remarks
Rat/Sprague-Dawley 5 females/dose; 5 males in top dose group only 1000, 2500, 5000 mg/kg OECD 402, GLP (Krötlinger, 1991 in Reference 2)	> 5000 mg/kg	The test substance was applied under occlusive conditions for 24 hours. There were no treatment-related deaths. There were no signs of local skin irritation. Clinical signs of toxicity included piloerection, apathy and laboured breathing. Necropsy did not reveal any treatment-related gross organ lesions.
Rats/Wistar 5/sex 2000 mg/kg OECD 402, GLP (Krötlinger, 2003b in Reference	> 2000 mg/kg	The test substance was applied under occlusive conditions for 24 hours. There were no treatment-related deaths. The only clinical signs observed were decreased motility and reactivity, uncoordinated gait and laboured breathing in one female. No gross pathological changes were observed.

2)		
Rats/unspecified strain 5 males 1000 mg/kg Not guideline or GLP (DuBois & Kinoshita, 1965 in Reference 2)	> 1000 mg/kg	There were no treatment-related deaths.

5.2.4 Summary and discussion of acute toxicity

The LD_{50} values (range from > 300 to 792 mg/kg) obtained from three acute oral toxicity studies were within the range (200-2000 mg/kg) for Xn; R22 (criteria in Directive 67/548/EEC).

These oral LD_{50} values were also within the range (300-2000 mg/kg) for acute toxicity category 4 (new criteria in the CLP Regulation).

In an acute inhalation toxicity study, fuberidazole was tested at the maximum concentration technically attainable, resulting in an LC_{50} of > 0.458 mg/L. Therefore, classification is not justified.

The LD_{50} values obtained from acute dermal application of fuberidazole were above the classification cut-off (2000 mg/kg) that applies in both Directive 67/548/EEC and the CLP Regulation. Therefore, no classification is proposed.

Directive 67/548/EEC:	**confirm Xn; R22**
CLP Regulation:	**propose Acute Tox. 4 (H302)**

5.2.5 Summary and discussion of specific target organ toxicity – single exposure

The clinical signs that were apparent after single oral and inhalation exposures to fuberidazole were indicative of non-specific, general acute toxicity. As there was no clear evidence of specific toxic effects on a target organ or tissue, no classification for specific target organ toxicity (single) under Regulation EC/1272/2008 is proposed.

5.3 Irritation

5.3.1 Skin

The potential of fuberidazole to cause skin irritation has been investigated in one standard study (Leuschner, 1999a in Reference 2). The test substance (500 mg) was applied to the shaved dorsal area of the trunk of three male Himalayan rabbits. Scores were taken at 60 minutes, 24, 48 and 72 hours after patch removal, with a post-treatment observation period of 14 days. There were no treatment-related findings (all scores were 0). The absence of irritation during the acute dermal studies in rats (section 5.2.3) provided supportive evidence.

5.3.2 Eye

The potential of fuberidazole to cause eye irritation has been investigated in a standard study in rabbits (Leuschner, 1999b in Reference 2). The test substance (100mg) was administered into the conjunctival sac of the right eye of male Himalayan rabbits. Scores were recorded at 1, 24, 48 and 72 hours after the administration. There were no treatment-related findings (all scores were 0).

5.3.3 Respiratory tract

No evidence of respiratory tract irritation was found in an acute inhalation study in rats (section 5.2.2).

5.3.4 Summary and discussion of irritation

Fuberidazole does not meet the criteria for classification as a skin irritant or an eye irritant. Therefore, no classification is proposed under Directive 67/548/EEC or the CLP Regulation. The available information does not indicate that fuberidazole is irritant to the respiratory tract.

Directive 67/548/EEC:	**no classification is proposed**
CLP Regulation:	**no classification is proposed**

5.4 Corrosivity

Fuberidazole was not corrosive when tested for skin and eye irritation.

Directive 67/548/EEC:	**no classification is proposed**
CLP Regulation:	**no classification is proposed**

5.5 Sensitisation

5.5.1 Skin

Table 3. Summary of skin sensitisation data

Species	Method	Doses	No. sensitised/total no.	Result
Guinea pig (males) 20 in treatment group, 10 in control groups (Heimann, 1984 in Reference 2)	Maximisation test OECD 406 (1981) Not GLP	*Induction* intradermal: 1% topical: 25% *Challenge*: 1st: 25% 2nd: 12.5% Formulated in paraffin oil	*1st challenge* 17/20 at 48 hours 13/20 at 72 hours *2nd challenge* 16/20 at 48 hours 10/20 at 72 hours No skin reactions in control animals	Sensitising
Guinea pig (males)	Open epicutaneous test	*4 week induction period*: 20 treatments with 3%, 10% or 30% formulation in	0/8 for all groups	Non-sensitising

8/group (Heimann, 1985 in Reference 2)	OECD 406 (1981) GLP	'Cremophor EL'/saline *Challenge*: 1% (control), 3%, 10% and 30%		

The potential of fuberidazole to induce skin sensitisation has been investigated by the same laboratory in two guinea pig tests.

In a maximisation test, positive results in ≥ 50% of animals were obtained after both the first and the second challenge at 48 and 72 hours. The scores ranged from 1 (slight erythema) to 3 (moderate confluent erythema) following each challenge. None of the negative control animals displayed any adverse skin reactions.

In an open epicutaneous assay, no skin reactions occurred in the test group animals. It was not reported if positive control animals were included or, if they were, if they responded appropriately.

5.5.2 Respiratory system

No information available.

5.5.3 Summary and discussion of sensitisation

Fuberidazole was positive in a guinea pig maximisation test but negative in a guinea pig open epicutaneous test; both tests were conducted in accordance with the contemporary OECD guideline 406 (1981). The maximisation test is generally considered to be the more rigorous and sensitive of these two types of test on account of the use of an adjuvant and an occlusive dressing and therefore the findings from this test are given precedence.

Given the clearly positive findings in the maximisation test (i.e. clear responses in greater than the required 30% of animals), a classification of Xi; R43 under Directive 67/548/EEC and of skin sensitisation category 1 (H317) under the CLP Regulation is proposed.

There is no available information on the potential of the test substance to induce respiratory sensitisation.

Directive 67/548/EEC:	**propose Xi; R43**
CLP Regulation:	**propose Skin Sensitisation Cat. 1 (H317)**

5.6 Repeated dose toxicity

Short-term repeated dose toxicity studies are available by the oral (rat, dog) and dermal (rabbit) routes.

5.6.1 Repeated dose toxicity: oral

5.6.1.1 Rat

Table 4.1. Short-term repeated dose studies in the rat

Dose schedule	Dose levels	Observations and remarks (effects of major toxicological significance)
Oral (gavage) 5 days/week for two months (60 days) Rats (unspecified strain), males, 10/group Not guideline or GLP (Hecht & Kimmerle, 1964 in Reference 2)	0, 15, 30, 60, 120, 240 mg/kg/d Purity not stated Vehicle 'Lutrol'	There were single mortalities (cause of death: pneumonia) at 15 and 120 mg/kg/d that were not treatment-related. Three animals in the high-dose group died in the first 5 days of treatment, but there was no description of their clinical signs. Gross necropsy of the livers, spleens, kidneys, adrenals and thyroids of all animals did not reveal any findings. There were no overt clinical signs of toxicity in the survivors. Liver weights (no further details) were increased at ≥ 120 mg/kg/d. Insufficient details from this study were available to assign a meaningful NOAEL. However, it is clear that no serious effects were seen at 60 mg/kg or less.
Oral (dietary) 4 months (120 days) Rats/FB 30, males and females 15/sex/dose Not guideline or GLP (Lorke & Löser, 1966 in Reference 2)	0, 150, 500, 1500, 4500 ppm Equivalent to Males: 0, 10.6, 35.4, 106.2, 318.5 mg/kg/d Females: 0, 14.25, 47.5, 142.5, 427.5 mg/kg/d Purity 83%	Treatment-related deaths occurred in males (0/15, 0/15, 0/15, 8/15 at 0, 150, 500, 1500 and 4500 ppm). These deaths were a result of increased susceptibility to disease, which the study authors attributed to the general poor condition and decreased food intake/body weights gains of these animals. The deaths in females were not treatment-related (2/15, 0/15, 0/15, 4/15, 2/15 at 0, 150, 500, 1500 and 4500 ppm). Body weight gain was reduced by 15% at 1500 ppm and 80% at 4500 ppm in males and females. The reduction in food consumption was particularly marked at 4500 ppm (56.2% to 66% reduction over the treatment period). There was a treatment-related effect on liver weights and histopathology. Relative liver weights were increased by 0%, 13%, 8%, 18%, 117% in males and 0%, -93%, -88%, 4%, 70% in females at 0, 150, 500, 1500 & 4500 ppm. At 4500 ppm (males and females), histopathological changes included: periportal (and sometimes midzonal) hepatocyte enlargement (nucleoli appeared prominent and strongly basophilic) in 5/5 males and 5/5 females; minimal bile duct reduplication in 4/5 males and 3/5 females. There were no degenerative liver changes. (The mg/kg/d equivalents are estimated, since these values were not provided in the study.) The NOAEL was 500 ppm (approximately 35 and 48 mg/kg/d in males and females, respectively) based on reduced body weight gain.

N.B. The values for NOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting.

In two short-term repeated dose studies in rats, doses of 120 mg/kg/d for 60 days and approximately 106/142 mg/kg/d for 120 days did not result in serious lesions. These doses are above the guidance values for a 90-day oral rat study for classification for repeated dose toxicity of > 5 ≤ 50 mg/kg/d that is specified in Directive 67/548/EEC and 10 – 100 mg/kg/d that is specified in the CLP Regulation. Serious effects only occurred at doses that were above these guidance values.

During the 60-day study in rats, there were deaths at 240 mg/kg/d that appeared to have been treatment-related, plus single deaths in some of the other treatment groups. The only other finding was increased liver weights from 120 mg/kg/d.

In the 120-day study, the changes in relative liver weight that were observed at approximately 106/143 mg/kg/d were considered to be adaptive, since they were small and not associated with histopathological changes. In contrast, the livers of animals exposed to 319/428 mg/kg/d showed large increases in liver weight that were associated with pathology. The minimal bile duct reduplication that was observed in this group was considered to be a result of hypertrophy in association with increased protein synthesis.

5.6.1.2 Dog

Table 4.2. Short-term repeated dose studies in the dog

<table>
<tr><th>Dose schedule</th><th>Dose levels</th><th>Observations and remarks
(effects of major toxicological significance)</th></tr>
<tr><td>Oral (dietary)
1 year
Dogs/beagle, males & females
4/sex/dose
OECD 452
GLP
(Schmidt & Gröning, 1994 in Reference 2; Rinke, 1996 in Reference 3)</td><td>0, 20, 100, 500 ppm
The highest dose was increased to 1000 ppm in week 27 then to 2000 ppm in week 41
Equivalent to
Males & females 0, 0.72, 3.6, 18/36/72 mg/kg/d (giving a weighted average of 36 mg/kg/d)</td><td>As there were no overt clinical signs of toxicity at 500 ppm, the highest dose was increased in week 27 then again in week 41.
One animal in the high-dose group died in the second week (and was replaced), but it had not exhibited clinical signs of toxicity and no cause of death or relationship to treatment could be established. Another animal in the high-dose group was euthanized in week 39 because of reduced food consumption, emaciation and deterioration in health (treatment-related). This animal had a lowered lymphocyte count, an increase in band granulocytes, and increased AST (by > 1000%), LDH (by 85%), creatinine kinase (by > 700%) and ALT (by > 200%) activity.
The survivors did not demonstrate clinical signs of toxicity, and their food consumption and body weight gains were unaffected.
Absolute liver weights were increased by 1%, -1%, 14% in males and 5%, 15%, 31% in females at 20, 100 & 500/1000/2000 ppm respectively. Liver weights relative to brain weight were also increased: 4%, -4%, 21% in males; 9%, 15%, 31% in females. These changes were not associated with changes in histopathology or morphology.
Heart weights were unaffected by treatment. However, there were increased incidences of gross and histopathological changes at ≥ 100 ppm. Gross changes included yellow dots, stripes or patches in the papillary muscles (1/8 dogs with the mid-dose, 4/8 with the high-dose). Histopathology revealed a dose-related increase in the incidence and severity[2] of focal fibrosis of the papillary muscles of the heart (left ventricle), as illustrated in the table below.
<table>
<tr><td></td><td></td><td colspan="4">Males</td><td colspan="4">Females</td></tr>
<tr><td colspan="2">mg/kg/d</td><td>0</td><td>0.72</td><td>3.6</td><td>18</td><td>0</td><td>0.72</td><td>3.6</td><td>18</td></tr>
<tr><td></td><td></td><td colspan="8">Section 1 (numbers with histopathology)</td></tr>
<tr><td>‘Left’[3]</td><td>minimal
slight
moderate
severe</td><td></td><td></td><td>2</td><td>2

1
1</td><td></td><td></td><td>1</td><td>1

3</td></tr>
</table>
</td></tr>
</table>

[2] The changes were graded as *minimal*: single area of fibrosis (< 0.5 mm) next to the insertion of the chordae tendineae in one or both papillary muscles; *slight*: single area of fibrosis (> 0.5 < 3 mm) next to the insertion of the chordae tendineae in one or both papillary muscles, or multifocal areas of fibrosis (< 0.5 mm) in one or both papillary muscles; *moderate*: multifocal areas of fibrosis (> 0.5 < 3 mm) in both papillary muscles, or single area of fibrosis (> 3 mm) in one or both papillary muscles; *severe*: multifocal areas of fibrosis (> 3 mm) in both papillary muscles. Not restricted to the insertion of the chordae tendineae but also in deeper parts of the muscle. Partly accompanied by adipose tissue.

[3] A defined relation of the papillary muscles to their anatomical origin was not possible retrospectively (these data are derived from a second examination of the heart tissues (Rinke, 1996 in Reference 3)). For identification during histology examination, the sample located close to the slide’s plate was named ‘right’ and the opposite sample ‘left’.

		'Right'	minimal				1	1		1	
			slight			2			1	1	1
			moderate				1			1	
			severe				2				3
				Section 2 (numbers with histopathology)							
		'Left'	minimal		1					1	
			slight			1	2				
			moderate			1	1				1
			severe				1			1	3
		'Right'	minimal			2	1				
			slight				1		1	2	1
			moderate				2			1	
			severe								3
				Section 3 (numbers with histopathology)							
		'Left'	minimal			2	1				
			slight				1				
			moderate				2			1	2
			severe								2
		'Right'	minimal								
			slight			3	1	1	1	2	
			moderate				2			1	
			severe				1			1	4
		Total incidence			1	13	24	2	3	14	24
		No. dogs affected		0	1	4	4	1	1	3	4

In the high-dose group, 6/8 dogs (including the animal that died at week 39) had lesions that were scored as severe. The remaining two dogs in this group had moderate lesions. In the mid-dose group, the changes were scored between minimal to severe (moderate in 3/8 animals, severe in 1/8 animals). In the one control dog that showed fibrosis, the changes were minimal to slight.

Some endocrine organs (thyroid, pancreas, adrenals) had increased relative (to brain) weights in males of the high-dose group (up to 20%). There were no associated histological changes.

Absolute and relative uterine weights were increased in the mid- and high-dose groups by 18 to 50%. Again, there was no correlation to histological changes.

The NOAEL was 20 ppm (0.72 mg/kg/d) based on increases in focal heart fibrosis incidence and uterine weight.

Oral (dietary) 1 year Dogs/beagle, males & females 4/sex/dose OECD 452 GLP (Schmidt & Popp, 1994 in Reference 2)	0, 5, 10 ppm Equivalent to approximately 0, 0.16, 0.32 mg/kg/d	Electrocardiogram test and blood pressure measurement were performed before initiation of the study and at weeks 5, 26 and 52 of treatment. General health, feed consumption, body weight gain, haematology, clinical chemistry and urinalysis were unaffected by treatment. There were no treatment-related findings in the electrocardiogram tests and blood pressure measurement. No substance-related findings were observed in the gross pathology, organ weight determination or histopathology investigations. There were no effects on the myocardium. The NOAEL was 0.32 mg/kg/d.
Oral (dietary) 90 day Dogs/beagle, males &	0, 50, 150, 450 ppm No mg/kg/d equivalents were	Survival was unaffected and there were no overt clinical signs of toxicity. No treatment-related effects were seen on food consumption, body weight gain, haematological and clinical chemistry parameters, gross pathology or

females, 2/sex/dose Not guideline or GLP (Löser, 1968 in Reference 2)	provided	organ weights. Histopathology was not conducted. A kidney function test that involved the administration of inulin and para amino hippuric acid followed by measurement of their clearance indicated that the kidney function was normal. The NOAEL was > 450 ppm (estimated to be equivalent to 11 mg/kg/d).
Oral (gelatine capsules) 26 to 29 days Dogs/beagle 2/sex/dose (Detzer & Sander, 1996 in Reference 2)	0, 5, 40, 200 mg/kg/d	The doses were administered to the low- and mid-dose groups for 29 days and to the high-dose group for 26 days. One animal of the high-dose group died on day 14, and the other animals in this group were killed *in extremis* on day 26. At ≤ 40 mg/kg/d there was no evidence of a cardiotoxic effect by ECG, blood pressure or pulse rate investigations. At 200 mg/kg/d blood pressure and pulse rates were reduced, but ECG did not show any effects on the heart function. No substance-related findings were noted in the heart muscle in any of the dose groups. This was supported by there being no change in the creatinine kinase levels in any of the groups. At 200 mg/kg/d liver enzymes (ASAT, ALAT, GLDH, alkaline phosphatase) were drastically increased by at least 500%; LDH and urea were moderately increased by at least 50%. Histology of the liver demonstrated severe hepatocellular injury with cytoplasmic vacuolation, lipid storage, liver cell degeneration and necroses and cholestasis in the high-dose group only.
Oral (gelatine capsules) 7 days Dogs/beagle 4 males/dose (Detzer, 1996 & Eiben, 2004 in Reference 2)	100 or 200 mg/kg/d	One animal of the 200 mg/kg/d group died on day 2. This animal had sub-endocardial haemorrhage and early autolytic changes but no evidence of myocardial lesions. The study authors did not postulate a clear explanation for these effects. In the survivors, ECG, blood pressure, pulse rate and histopathological investigations of the left ventricular papillary muscle gave no indications of a specific cardiotoxic effect.

N.B. The values for NOAEL and LOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting

Five repeated-dose studies have been conducted in dogs, with durations ranging from seven days to one year.

Following administration of fuberidazole for one year at doses of 3.6 mg/kg/d and above, histopathology of the heart revealed fibrotic areas in the myocardium of the papillary muscles in all treatment groups. These fibrotic areas were generally located close to the insertion of the chordae tendineae. The heart sections were stained in a way to enable differentiation between lesions such as the very small induced fibrotic areas that were noted in the 0.72 mg/kg/d group, and the more serious lesions of the perivascular connective tissue or in the area of insertion of the chordae tendineae into the papillary muscles. The effects in the 0.72 mg/kg/d group were minimal/slight and of a similar frequency to those in the controls; they were not considered to be treatment related. However, the increased incidences and severities in the 3.6 mg/kg/d and 36 (average) mg/kg/d groups were toxicologically significant. There were two deaths in the high-dose group, one of which was clearly related to treatment. The increase in creatinine kinase noted in this dog was indicative of a toxic effect on muscular tissue and was consistent with myocardial damage. Histopathology investigations on this dog revealed changes in the testes (desquamation, megakaryocytes), epididymides (desquamation of germinal epithelia, oligo spermatism), prostate

(immaturity and cellular infiltration), thymus (atrophy), gall bladder (oedema) and urinary bladder (cellular infiltration).

Because of the absence of histopathology investigations, it was not possible to conclude if any cardiac effects occurred when fuberidazole was administered for 90 days. Administration for shorter durations (seven to 29 days) did not result in adverse cardiac effects. However, deaths and severe liver toxicity were apparent with doses of 200 mg/kg/d fuberidazole for up to 29 days. At lower doses (weighted average 36 mg/kg/d) administered for up to one year, increases in liver weights occurred but were considered to be related to metabolic adaptation. There was no clear explanation for the weight changes in the endocrine organs or the uteri observed in the animals that received an average of 36 mg/kg/d fuberidazole for one year.

5.6.2 Repeated dose toxicity: inhalation

No information available.

5.6.3 Repeated dose toxicity: dermal

Table 4.3. Repeated dose dermal study in the rabbit

Dose schedule	Dose levels	Observations and remarks (effects of major toxicological significance)
Dermal 14 days Rabbits/chinchilla, males & females, 5/sex/dose Not guideline or GLP (Kimmerle, 1970 in Reference 2)	0 or 250 mg/kg/d administered in 'Lutrol' & applied to shorn dorsal skin under a semi-occlusive dressing Dose applied daily for 24 hours No purity specified	No mortalities or overt clinical signs of toxicity occurred (the animals were observed for 2 weeks post-treatment). The NOAEL was > 250 mg/kg/d.

N.B. The values for NOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting

A single, short-term dermal repeated dose study is available in rabbits. Only one dose was tested (250 mg/kg/d). No clinical signs were noted, and there were no changes in body weight gain; haematology (haemoglobin concentration, erythrocyte count, mean corpuscular haemoglobin concentration, leukocyte count, thrombocyte count, haematocrit, mean corpuscular volume); clinical chemistry (AST, ALT, SDH, total bilirubin and total protein); urinalysis; and kidney function tests. No histopathology was performed on the organs.

5.6.4 Other relevant information

One study has been conducted to investigate the toxicokinetics of fuberidazole in dogs.

Table 4.4. Toxicokinetic investigation in dogs

Dose schedule	Dose levels	Observations and remarks (effects of major toxicological significance)
Oral (not stated if gavage or gelatine capsules)	0, 5, 40, 200 mg/kg/d	There were often disproportionately large rises in C_{max} for an 8- and 40-fold increase in dose, particularly in males (C_{max} 48, 2962, 6121 ng/ml at 5, 40 & 200 mg/kg/d). However, in all dose groups low plasma concentrations were measured by 4-7 hours after administration.

4 weeks Dogs/beagle 2/sex/dose (Schmidt, 1996 in Reference 2)		In week 4 the metabolic capacity was saturated in the high-dose group animals, as the plasma levels were about 2 x higher compared with the levels reached on day 1. Additionally, the percentage of unmetabolised fuberidazole excreted in urine was 10-38% of the administered dose, compared with < 0.2% at the lower dose levels.

A toxicokinetic study demonstrated that fuberidazole was quickly metabolised and eliminated via urine at low to moderate dose levels, but that the metabolic capacity was exceeded at 200 mg/kg/d; this may have explained the severe liver toxicity that was observed at this level. A noticeable metabolic effect resulted in the excretion of a relatively large proportion of unmetabolised fuberidazole when a high dose (200 mg/kg/d) was administered. Repeated oral high doses were not administered to rats for the toxicokinetic investigations, so it is not known if saturation of the metabolic capacity may also occur in this species (see section 5.1).

5.6.5 Summary and discussion of repeated dose toxicity

Some of the available repeated dose studies are old and lacking in sufficient information for a full evaluation of fuberidazole's repeated dose toxicity. However, a pattern of liver or cardiac toxicity emerged from those studies that were of a better quality.

When administered by the oral route in high doses to rats (318/427 mg/kg/d) and dogs (200 mg/kg/d), the target organ of fuberidazole was the liver. Since the liver toxicity occurred only at doses that were well above the guidance values for 90-day studies in rats, these effects do not meet the criteria for classification for repeated-dose toxicity. In two-year studies in rats and mice, liver toxicity (histopathological findings) was also observed (section 5.8). However, again, these findings only occurred at relatively high dose levels (122 mg/kg/d in rats and 150 mg/kg/d in mice) and so are of no relevance for classification.

In dogs, when fuberidazole was administered orally at moderate-to-low doses (from 3.6 mg/kg/d) for one year, the heart was the main target organ. Mortality also occurred at 18/36 mg/kg/d. Classification may be warranted based on these effects.

Dermal administration of fuberidazole in a short-term repeated dose study did not result in any adverse effects.

5.6.5.1 Classification rationale

The criteria for classifying a substance for repeated dose toxicity under Directive 67/548/EEC and the CLP Regulation state that, for this classification to be applied, a substance should cause serious damage (clear functional disturbance or morphological change which has toxicological significance) on repeated or prolonged exposure below the specified guidance values.

In a one-year dog study, the most toxicologically important finding was an increased incidence of fibrosis of the left ventricular papillary muscles at 3.6 and 36 (average) mg/kg/d in males and females, together with one treatment-related death at 18/36 mg/kg/d. At these doses the fibrosis was graded as moderate (multifocal areas in both papillary muscles or single area > 3mm in one or both papillary muscles) or severe (multifocal areas of fibrosis > 3 mm in both papillary muscles). Moderate lesions occurred in 3/8 dogs at 3.6 mg/kg/d and 2/8 dogs at 36 (average) mg/kg/d. Severe lesions occurred in 1/8 dogs at 3.6 mg/kg/d and 6/8 dogs at 36 (average) mg/kg/d. Therefore, based on the evidence of severe organ damage (multifocal fibrosis) and one substance-related death, it is proposed that fuberidazole should be classified for repeated dose toxicity by the oral route.

In deciding whether a classification as Toxic or Harmful is most appropriate based on this dog data, it is useful to consider the overall picture of the toxicity. Although there was one substance-related death, the remaining animals did not exhibit clinical signs of toxicity or illness, even at the highest dose. Gross cardiac changes were observed only at the highest dose, and histopathology was necessary before the fibrosis of the papillary muscles became apparent. It should also be noted that these effects were observed only after long-term exposures (one year) and were not present in shorter-term studies (29 days) with higher doses.

For these reasons, based on the focal fibrosis of the heart observed in a one-year oral dog study at doses of 3.6 mg/kg/d and above, a classification of Harmful for repeated dose toxicity (Directive 67/548/EEC) and of specific target organ toxicity (repeated exposure) Category 2 (CLP Regulation) is proposed.

No classification by the dermal or inhalation routes is proposed.

Directive 67/548/EEC:	**propose Xn; R48/22**
CLP Regulation:	**propose STOT RE 2 (heart); H373**

5.7 Mutagenicity

Benzimidazole fungicides are widely considered to exert their effects through binding to free tubulin, particularly β-tubulin at the colchicine binding site, which disrupts microtubule formation and thereby inhibits mitosis. A number of mutagenic benzimidazoles (e.g. carbendazim and benomyl) have also been shown to inhibit mammalian tubulin polymerisation and to be aneugenic *in vivo*. Because of this, particular attention was paid to the possibility that fuberidazole may have these effects in *in vitro* and *in vivo* genotoxicity studies.

Table 5.1. Summary of in vitro genotoxicity data

Method	**Organism/strain**	**Concentrations tested**	**Result**
Bacterial reverse mutation (Ames) Similar to OECD 471. Not GLP (Herbold, 1980a in Reference 2)	*S. typhimurium* TA98, 100, 1535, 1537	20 to 5000 µg/plate	**Negative** ± S9 metabolic activation Precipitation of the test substance occurred at concentrations above 5000 µg/plate
In vitro mammalian cell gene mutation test OECD 476. GLP (Lehn, 1988 in Reference 2)	Chinese hamster ovary cells (*hprt* locus)	12.5 to 250 µg/plate	**Negative** ± S9 metabolic activation Precipitation of the test substance at 250 µg/ml (without activation). With activation, increasing cytotoxicity occurred with increasing concentrations.
In vitro chromosome aberration test OECD 473. GLP	Chinese hamster ovary cells	16.7 to 500 µg/plate	**Negative -** metabolic activation **Positive** + S9 metabolic activation Cells were exposed to the test substance for 2

(Taalmann, 1987 in Reference 2)			hours then sampled after 24 hours. The positive responses occurred at concentrations that resulted in cytotoxicity (> 100 µg/ml). Cytotoxicity was evidenced by a 70-80% reduction in monolayer confluency and an almost complete cessation of mitosis, and occurred with and without metabolic activation (0% cells at 166.7 and 500 µg/ml ±S9 completed more than one cell cycle). The test substance produced strongly positive responses with metabolic activation (statistically significant).
In vitro unscheduled DNA synthesis test OECD 482. GLP (Lehn, 1989 in Reference 2)	Primary rat hepatocytes	5 to 100 µg/plate	**Negative** The positive control substance produced the appropriate response.
In vitro micronucleus assay Draft OECD 487. GLP (Kumaravel, 2005 in Reference 4)	Human peripheral blood lymphocytes from two donors In the repeat experiment one donor was different Blood was pooled rather than cultured separately	25 to 500 µg/ml	**Equivocal** – metabolic activation **Positive** + S9 metabolic activation The cells were exposed to the test substance for 20 hours (-S9) or 3 hours (+S9) then harvested 24 hours (experiment 1) or 48 hours (experiment 2) after mitogenic stimulation. Positive responses (statistically significant) occurred only in the 2nd experiment. Without metabolic activation, the increases in micronuclei were at the outer limit of historical control values. With metabolic activation, the increases were considered to be biologically relevant by the study authors.

Table 5.2. Summary of in vivo genotoxicity data

Method	**Organism/strain**	**Concentrations tested**	**Result**
Chromosome aberration assay OECD 475. GLP (Whitwell, 2007 in Reference 4)	Rat/Wistar (6 males/group)	Single dose of 0, 75, 150, 300 mg/kg (oral by gavage)	**Negative** Bone marrow was sampled 17 and 42 hours after administration of the dose. One animal in the high-dose group died. A 48% reduction in the mitotic index of the high-dose group indicated that the bone marrow cells had been adequately exposed.
Micronucleus assay (oral) Similar to OECD 474 Not GLP (Herbold, 1980b Reference 2)	Mouse / NMRI (males and females, 5/sex/group)	2 x 100 mg/kg 2 x 200 mg/kg 24 hour intervals between dosing	**Negative** The bone marrow was investigated. No information was provided on the effects of treatment on the PCE/NCE ratio. An appropriate response was obtained from the positive control substance.
Micronucleus assay (i.p.) OECD 474. GLP (Herbold, 1990a	Mouse / NMRI (males and females, 5/sex/group)	1 x 150 mg/kg	**Negative** The bone marrow was investigated at 24, 48 and 72 hours after administration of the dose. The animals showed signs of toxicity but the PCE/NCE

Reference 2)			ratio was not altered.
Sister chromatid exchange test US EPA guideline. GLP (Herbold 1990b Reference 2)	Hamster / Chinese (5/sex/dose)	0, 25, 50, 100 mg/kg (i.p.)	**Negative** Bone marrow cells investigated. No treatment-related effects on the mitotic index or the ratios of 1st, 2nd or 3rd metaphases, or the frequency of sister chromatid exchanges.
Germ cell effects (rodent dominant lethal assay) Not guideline or GLP (Machemer, 1974 in Reference 2)	Mouse / NMRI (20 animals)	150 mg/kg (oral)	**Negative** Each male mouse was mated with 3 untreated females per week for 8 weeks. The females were investigated on gestation day 14 for pre- and post-implantation loss, corpora lutea, number of implantations, number of viable and dead foetuses.

5.7.1 *In vitro* data

Fuberidazole has been investigated in five *in vitro* studies that test the potential of substances to cause bacterial cell mutation, mammalian cell mutation, clastogenicity and DNA damage. Three of these were negative, whereas the chromosome aberration test and the *in vitro* micronucleus assay gave positive results.

In the chromosome aberration study in Chinese hamster ovary cells, statistically significant increases in aberrant cells (chromosome and chromatid rearrangements) occurred at concentrations of test substance that resulted in cytotoxicity (70 to 80% reduction in monolayer confluence). However, it was not possible to dismiss these positive results as an artefact of the high cytotoxicity, since the clastogenic effects did not occur without metabolic activation, even though the cytotoxicity occurred at the same level as with metabolic activation. In this study, fuberidazole also caused a cessation of mitosis (at cytotoxic doses), which may be consistent with the spindle inhibiting properties of benzimidazoles.

In the *in vitro* micronucleus assay in human peripheral blood lymphocytes, increases in micronuclei binucleate cells occurred in only one of the two repeats, with those observed in the presence of metabolic activation being considered as biologically relevant. There were two differences between the conduct of the repeat experiments that may have accounted for the discrepancy in the results: firstly, the positive experiment commenced 48 hours after mitogenic stimulation, rather than 24 hours after, as was the case for the negative experiment; secondly, one of the donors differed between the experiments.

The *in vitro* micronucleus assay was then extended to investigate the mechanism of action of the positive finding. Fluorescence *in situ* hybridisation (FISH) of fuberidazole-exposed micronucleated binucleate cells showed that the frequency of centromere-positive cells was in the range of the vehicle control cells (4-12%, in contrast to cells exposed to the aneugen vinblastine, where > 86% of cells had a centromere). The majority of micronuclei were therefore induced by breakage of chromosomes (clastogenicity) rather than the loss of whole chromosomes (aneugenicity).

5.7.2 *In vivo* data

In a recently-conducted *in vivo* chromosome aberration assay, there were almost no structural aberrations in any of the test groups, and only a few gaps. The numerical aberrations were restricted to occasional incidences of polyploidy, which were not higher than the control groups.

This test supported data from two *in vivo* micronucleus assays that were also negative. A sister chromatid exchange assay gave further reassurance that the chromosome and chromatid rearrangements that were observed *in vitro* did not occur *in vivo*.

Based on the results of a rodent dominant lethal assay, fuberidazole did not have any germ cell effects.

In view of an acute oral LD_{50} of between 200 and 500 mg/kg, the dose levels used in all these *in vivo* studies appeared to be adequate.

5.7.3 Human data

No information available.

5.7.4 Other relevant information

5.7.5 Summary and discussion of mutagenicity

The tests reviewed for the initial Pesticide Assessment Report (Reference 2) were not considered to adequately address fuberidazole's potential inhibitory effect on mitosis, particularly in view of there being no polyploidy investigations. As a result, two new studies were submitted by the notifier (an *in vitro* micronucleus assay and an *in vivo* chromosome aberration assay, both included in Reference 4) and were considered to address this issue and to fulfil the data requirements of Directive 91/414/EEC.

The genotoxic potential of fuberidazole has been explored in five *in vitro* tests; it induced clastogenicity in two of these (a cytogenetics assay in mammalian cells and micronuclei analysis of human peripheral blood lymphocytes) in the presence of metabolic activation. Consistent results were not obtained between the two experimental repeats of the micronucleus assay, which may have been explained by differences in the ways the repeats were conducted. Fuberidazole also caused an almost complete cessation of mitosis in Chinese hamster ovary cells (at doses that were cytotoxic), which is in accordance with the spindle-inhibiting properties of benzimidazoles.

Fuberidazole was negative in five *in vivo* assays, including those that examined the clastogenic potential of substances. Although chromatid rearrangements occurred *in vitro*, they did not occur *in vivo*. Additionally, there was no polyploidy in an *in vivo* chromosome aberration assay. The doses administered were adequate for the test substance to have reached the target tissues.

Fuberidazole did not exhibit any germ cell mutagenic effects in a rodent dominant lethal assay.

In conclusion, fuberidazole was a clastogen *in vitro* in the presence of metabolic activation. However, it demonstrated no clastogenic activity *in vivo*, and so the *in vitro* finding is not considered to be of relevance to humans. Despite the spindle-inhibiting properties of benzimidazoles, fuberidazole did not show any aneugenic potential either *in vitro* or *in vivo*.

No classification is proposed under Directive 67/548/EEC or the CLP Regulation.

Directive 67/548/EEC:	**no classification is proposed**
CLP Regulation:	**no classification is proposed**

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

The oral carcinogenicity of fuberidazole has been investigated in rats and mice.

5.8.1.1 Rat

Table 6.1. Rat combined chronic/carcinogenicity study

Dose schedule	Dose levels	Observations and remarks (effects of major toxicological significance)
Oral (dietary) 2 years (inc. 1 year interim) Rats/Wistar, males & females 60/sex/dose (10/sex/dose used for interim necropsy at 1 year) OECD 453 GLP (Eiben, 1993 in Reference 2; Appendix 4b in Reference 3)	0, 80, 400, 2000 ppm Equivalent to Males: 0, 4.6, 23, 122 mg/kg/d Females: 0, 5.8, 29, 155 mg/kg/d	Survival was similar in all groups (> 50% at completion of the study). Treatment-related clinical signs were not observed. *Non-tumour findings*: body weights were reduced in the high-dose group animals throughout the study (by 10% in males and 6% in females at the end of the study). These differences were statistically significant. Food consumption was not affected by treatment. There were marginal increases in relative liver weights of females in the high-dose group only (11% at terminal investigation). However, relative liver weight was decreased by 8% in the female mid-dose group. At 2000 ppm the livers of both sexes showed visible colour changes. Histopathology at the terminal investigation showed that there were basophilic foci (in 6%, 6%, 4%, 44% males & 35%, 39%, 46%, 74% females at 0, 80, 400, 2000 ppm), eosinophilic foci (in 0%, 2%, 8%, 12% males & 4%, 6%, 4%, 4% females) or clear cell foci (in 74%, 67%, 71%, 84% males & 16%, 8%, 12%, 34% females). Hepatocellular hypertrophy was also increased in a dose-dependent fashion in males (periacinar, 0%, 0%, 10%, 88% at 0, 80, 400, 2000 ppm) and females (periacinar, 0%, 0%, 0%, 20%; centricinar, 4%, 0%, 0, 50%). Oval cell proliferation (10%) and increased mitosis (12%) were observed in females of the 2000 ppm group (compared with 0% in controls and other treatment groups). *Uterine tumours:* malignant endometrial adenocarcinoma occurred in 0/49, 4/49, 2/49, 5/50 females (0%, 8%, 4%, 10%) at 0, 80, 400, 2000 ppm. There were no such findings in the cervix. When historical control data (same laboratory) for Wistar rats was investigated, it was found that for data from the preceding 3 years, the range of uterine/cervical adenocarcinoma (there was no differentiation between those in the uterus and those in the cervix) was 0-8%; the incidence in the current study was greater by one animal only. For historical control data from the preceding 10 years, the highest incidence in the current study was equalled or exceeded in 4/36 studies. The RITA* database listed the historical control range for uterine adenocarcinomas from the same laboratory as 2-10% over the three years either side of this study (8 studies). *Thyroid tumours:* benign follicular cell adenoma occurred in 2/50, 2/49, 0/50, 2/50 males (4%, 4%, 0%, 4%) and 0/49, 1/49, 0/50, 4/50 females (0%, 2%,

		0%, 8%) at 0, 80, 400, 2000 ppm. The maximum historical control incidence (same laboratory) for the preceding 10 years in female Wistar rats was 2% (1 of approximately 50 animals in 8/29 studies, no occurrences in the other studies). The RITA* database showed that for this tumour type, the historical control range collected between 1986 and 1997 from the same laboratory was also 0-2% (15 studies). Histopathology of the thyroids did not indicate that they had increased functional activity. The NOAEL for neoplastic effects was 400 ppm (29 mg/kg/d) based on the incidence of uterine and thyroid tumours in females.

N.B. The values for NOAEL and LOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting.

**Registry of Industrial Toxicology Animal data. This is a database of historical control data from animal carcinogenicity and chronic studies collected from European companies and maintained by the Fraunhofer Institute of Toxicology and Experimental Medicine.*

(i). Non-tumour findings

In a two-year oral (dietary) study in rats, the target organ was the liver. This manifested as basophilic, eosinophilic and clear cell foci, together with hepatocellular hypertrophy. Liver enzymes were not measured, but these histopathology changes noticed in the liver at both the interim (12 month) and the terminal investigations may have been an indication of adaptive change as a result of hepatic enzyme induction. Although oval cell proliferation (which may indicate hepatotoxicity) and increased mitosis were noted, specific measurement or counting of these was not performed, but rather they were graded semi-quantitatively as ‘minimal’ or ‘slight change’.

(ii). Malignant uterine tumours

The increased incidence of malignant uterine tumours in the high-dose female group was statistically significant compared with the controls. However, they did not occur in a clear dose-response relationship. Moreover, the incidence of this tumour type in the high-dose females was within the observed range of the historical control data from the same laboratory collected over the three years either side of this study.

(iii). Benign thyroid tumours

The incidence of thyroid tumours showed a statistically significant positive trend in female rats. In addition to those female animals with thyroid tumours, a further female had slight focal follicular cell hyperplasia, and three females had follicular cysts lined with basophilic epithelium. The incidence of these benign thyroid tumours in the high-dose females (8%) was greater than in any of the historical control data studies from the same laboratory over the nine years that spanned this study (RITA database 1986 to 1997, maximum of 2%; data compiled from 15 studies). One potentially common cause of thyroid tumours in rodents is liver enzyme induction. However, in this study there were no histopathological findings to indicate that the thyroid gland had increased functional activity, and so a link to liver enzyme induction could not be made (although liver enzymes were not measured). Thus, the rat thyroid tumours observed in this study are considered to be of toxicological relevance.

5.8.1.2 Mouse

Table 6.2. Mouse combined chronic/carcinogenicity study

Dose schedule	Dose levels	Observations and remarks
Oral (dietary) 2 years (inc. 1	0, 100, 600, 1800 ppm	Survival was not affected by treatment (> 50% at 18 months, generally > 24% at 2 years, except for the low-dose females, where it was 18%). There were no

year interim) Mice/NMRI, males & females 60/sex/dose (10/sex/dose used for interim necropsy at 1 year) Mainly follows OECD 451, not GLP (Brune, 1983; Eiben, 2004 in Reference 2)	Equivalent to Males: 0, 25, 150, 466 mg/kg/d Females: 0, 29, 177, 551 mg/kg/d	overt clinical signs of toxicity. *Non-tumour findings*: body weight, food consumption, haematological and clinical chemistry, and urinalysis were not affected by treatment. Absolute liver weights were increased in males by 23%, 32%, 88% and in females by 23%, 25%, 61% at 100, 600 & 1800 ppm, respectively. Liver weights relative to brain weight were also increased in males (by 20%, 28%, 83%) and females (by 21%, 25%, 65%) in all dose groups. Histopathology was performed on all survivors at 2 years and on animals that died during the course of the study. This showed that there was an increased incidence of liver cell necrosis at doses of ≥ 600 ppm: focal necrosis in 14%, 6%, 38%, 48% of males and 12%, 20%, 30%, 28% of females; single cell necrosis in 0%, 0%, 8%, 12% of males and 2%, 6%, 0%, 12% of females at 0, 100, 600, 1800 ppm, respectively. *Liver tumours:* hepatocellular adenoma occurred in 1/50, 1/50, 3/50, 12/50 males (2%, 2%, 6%, 24%) and 0/50, 0/50, 1/50, 2/50 females (0%, 0%, 2%, 4%) at 0, 100, 600, 1800 ppm. The historical control range (from a different laboratory) for males from 13 studies finishing two years on either side of this study was 0 to 18% (mean 5%, median 4%); the historical control range for all studies in the RITA database was 2-16% (6 studies conducted between 1984 and 1996). For females, the historical control range from 13 studies finishing two years on either side of this study was 0 to 2% (mean 0.15%, median 0%); for 21 studies finishing three years on either side of the present study, the range was 0 to 4% (mean 0.57%, median 0%). There were no other tumour findings of note in the fuberidazole-exposed animals. The NOAEL for neoplastic effects was 600 ppm (150 mg/kg/d) based on the incidence of hepatocellular adenomas in males.

N.B. The values for NOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting

(i). Non-tumour findings

In a repeated dose (two year) oral study in mice, the target organ for fuberidazole was the liver. Toxicologically and statistically significant increases in absolute and relative liver weights occurred in all dose groups, which was accompanied by hepatocyte necrosis in the mid- and high-dose groups. Histopathology information was collected throughout the course of the study on all animals that died, but if one looks at the terminal sacrifice only, focal hepatocyte necrosis occurred in 2/26, 3/25, 14/27, 22/45 (8%, 12%, 52%, 49%, males and females combined) at approximately 0, 27, 164 and 509 mg/kg/d, respectively.

(ii). Benign liver tumours

Males of the high-dose fuberidazole group had an increased incidence of hepatocellular adenoma, which was in excess of the historical control data. In females, the incidence of these benign tumours was outside the historical control range by the equivalent of one animal for data taken from studies that were finished two years on either side of the fuberidazole study. If the historical control data is extended to three years either side of this study, the increased incidence in the high-dose female group was within the historical control values.

The liver tumours only occurred in the presence of hepatotoxicity. The increased incidence of the tumours in males of the high-dose group is consistent with the high incidence of hepatotoxicity in these animals: 48% of them had focal necrosis of the liver, and their relative liver weight was increased by 83% compared with the negative controls.

There is uncertainty around the mechanism of tumour induction in this study, as fuberidazole was negative in the genotoxicity assays, but one possible non-genotoxic mechanism is cytotoxicity

(Reference 5): the continual hepatocyte death results in persistent regenerative growth, which provides increased opportunities for spontaneous DNA mutations and the accumulation and proliferation of mutated cells. To define cytotoxicity as a mode of action in the induction of liver tumours, it is necessary to establish that there are parallel dose responses for both hepatotoxicity and proliferation. The tumours in this study were associated with hepatotoxicity, but cellular proliferation was not measured. Consequently, there remains some doubt about the mechanism(s) that led to the increased benign liver tumours seen with fuberidazole.

Mice appeared to be particularly susceptible to the hepatotoxicity compared with rats and dogs: in long-term studies in mice, liver weights were significantly increased even at the lowest dose (25 mg/kg/d), whilst severe hepatoxicity (necrosis) occurred from 150 mg/kg/d; whereas in the two-year rat study, only slight liver weight increases and changes in histopathology (mainly adaptive) were observed at approximately 155 mg/kg/d; and in dogs (one-year study), there were liver weight increases but no indications of cytotoxicity at the highest dose tested (weighted average 36 mg/kg/d). Male NMRI mice are also known to have an intermediate susceptibility to spontaneous liver tumour formation (Reference 6), which may explain why the incidence of this tumour type in this study was higher in the males than in the females.

5.8.2 Carcinogenicity: inhalation

No information available.

5.8.3 Carcinogenicity: dermal

No information available.

5.8.4 Carcinogenicity: human data

No information available.

5.8.5 Other relevant information

Studies to investigate the potential of fuberidazole to initiate and promote tumours were conducted in the 1980s, as summarised in the following table.

Table 6.3. Assays for promotion and initiation potential

Dose schedule	Dose levels	Observations and remarks
Initiation potential Rats/Wistar, 39/sex/dose Oral (gavage) (Schulte-Hermann, 1989 in Reference 2)	70 mg (single dose) administered 14 hours after partial hepatectomy	Solvent (maize oil) or N-nitrosomorpholine (NNM) were used as the negative and positive control, respectively. Five rats in each group then received a standard diet, and 8 rats received the same diet plus phenobarbitol (to act as a promoter). Putative pre-neoplastic foci in the liver were identified at sacrifice (10 weeks after partial hepatectomy). Fuberidazole did not significantly increase the number of foci in either sex, with or without phenobarbitol. NNM had a pronounced initiating effect.
Promotion potential Rats/Wistar 55/sex/dose	0.2, 2, 20, 80, 200 mg/kg/d for 3 months	Rats received a single oral (gavage) dose of 250 mg/kg NNM (initiation). Fuberidazole (or phenobarbital for the positive controls) was then administered in the diet for 3 months. After sacrifice, putative pre-neoplastic foci in the liver were identified by means of a positive gamma-glutamyl-transferase (CGT) reaction or by other cytological markers. The strength of

Oral (diet) (Schulte-Hermann, 1989 in Reference 2)		phenotypic expression of response (CGT positivity and demarcation from surrounding liver tissue) was used to place the responses into one of four categories. In males that had received fuberidazole, there was a statistically significant dose-related trend towards increased foci numbers. Treatment did not significantly increase the category into which these foci were placed or the area or volume affected. In females that received 200 mg/kg/d, there was a statistically significant increase in the parameters studied (foci number and volume, strength of phenotypic response). Phenobarbital clearly enhanced the number of foci and their total area or volume per unit liver tissue.

Fuberidazole was negative in a test for tumour initiation in rat liver. It had a slight tumour promotion effect on liver cells at a high dose, which is consistent with a non-genotoxic mode of carcinogenesis. In this context, promoting agents appear to act in two ways: 1) to selectively enhance cell replication in pre-neoplastic cells in altered hepatic foci; and 2) to inhibit apoptosis in pre-neoplastic cells. Model systems in rats and mice that investigate the initiation and promotion effects of chemical substances are generally regarded as being of relevance to humans (reviewed in Reference 5).

5.8.6 Summary and discussion of carcinogenicity

Chronic administration of fuberidazole resulted in increased incidences of benign thyroid tumours in rats and benign liver tumours in mice.

The thyroid follicular cell adenomas occurred only in the high-dose female rats (155 mg/kg/d) and at a relatively low incidence (8%, compared with a maximum of 2% in the most relevant historical control data). Distribution studies in rats demonstrated that high levels of fuberidazole were achieved in the thyroid after oral administration (section 5.1). Fuberidazole was non-mutagenic in the available *in vitro* and *in vivo* studies, but no further information on the mechanism of thyroid tumour formation is available.

Hepatocellular adenomas were increased in male mice of the high-dose group only (466 mg/kg/d) and with an incidence (24%) that was slightly greater than that of the historical control data range (18%). The tumours were associated with liver necrosis. Considering all the available repeated-dose toxicity data, the mouse liver appeared to be more susceptible to fuberidazole-induced toxicity than did that of rats and dogs. Therefore, there is a possibility that the mouse is more sensitive for liver toxicity caused by fuberidazole.

In the absence of any robust mechanistic explanations for how these tumours were induced, it is difficult to dismiss their relevance to humans. However, they appear to have been induced by non-genotoxic mechanisms. Also, as the liver tumours were specific to male mice (and were associated with hepatoxicity) and the thyroid tumours were restricted to female rats, they seem to be sex- and species-specific.

5.8.6.1 Classification rationale

Fuberidazole induced two tumour types in two species. Therefore, the question is whether these tumours provide sufficient evidence to justify the classification of fuberidazole for carcinogenicity.

Because there is no human evidence that fuberidazole is carcinogenic, Category 1 (Directive 67/548/EEC) is not appropriate. Although positive results were obtained in two animal species, both

the tumours types were benign in nature, sex-specific and occurred in low incidences only at high, relatively toxic doses. There were no robust mechanistic studies to explain their induction, but the mechanism was non-genotoxic. Therefore, the level of concern for humans is low and Category 2 is not appropriate.

Looking specifically at the criteria for deciding between Category 3 and no classification, there are three different aspects that may lead one to decide that a substance should not be classified. The first of these is if a mechanism of tumour induction has been identified that cannot be extrapolated to humans. In the case of fuberidazole, the liver tumours in mice were clearly associated with hepatotoxicity, with the mouse appearing to be more sensitive to the liver toxicity than the other investigated species. The second aspect is the occurrence of liver tumours in sensitive strains of mice, in the absence of other tumour types or supplementary information. Although the NMRI mouse strain is not the most sensitive strain for liver tumour induction, neither is it the least sensitive, and the increased incidence only in the males was consistent with males of this strain having a higher susceptibility than the females; additionally, the tumours were only induced in conjunction with hepatoxicity. The third aspect to be considered is whether the induced tumours occur at sites and in strains of animals where they are known to occur spontaneously with a high incidence. Benign tumours are common in the thyroid and liver of rats and mice. Further considerations are that the tumours were species- and sex-specific in single tissues.

Therefore, the evidence points towards the tumours being of limited or no relevance to humans, and the overall conclusion is that fuberidazole should not be classified for carcinogenicity

Directive 67/548/EEC:	**no classification is proposed**
CLP Regulation:	**no classification is proposed**

5.9 Toxicity for reproduction

The reproductive toxicity of fuberidazole has been investigated in a multi-generation fertility/developmental study and in three developmental toxicity studies.

5.9.1 Effects on fertility

A two-generation study has been conducted in rats. The fertility effects described in this study are summarised in the table below, since the classification criteria specify that effects on fertility may occur on the stages up to and including implantation. The developmental effects are included in section 5.9.2.

Table 7.1. Two-generation study

Dose schedule	Dose levels	Observations and remarks (effects of major toxicological significance)
Oral (dietary) 2 generation Rats/Wistar 25/sex/dose OECD 416	0, 50, 250, 1250 ppm Actual intakes Males: 0, 4, 20, 103 mg/kg/d	*Parental toxicity*: body weight gain of the high-dose F_0 males was reduced by approximately 20% at week 4. At sacrifice this difference had reduced to about 5%. The terminal body weights of the F_{1B} adults were unaffected by treatment. The relative liver weights of the F_{1B} females were statistically significantly increased in the high-dose group (by 3%, 4%, 18% at 50, 250, 1250 ppm). Relative liver weights were also increased in the F_0 animals in response to treatment (0%, 5%, 5%, 7% in males and 0%, 0%, -3%, 12% in females at 0, 50, 250, 1250 ppm), although these changes were not always

GLP (Holzum, 1989 in Reference 2)	Females: 0, 5, 25, 132 mg/kg/d Administered from at least 105 days before mating of F_0 animals until sacrifice of the F_1 animals (at weaning of F_2)	statistically significant. No histological correlates to the increased liver weight could be determined, and there were no other treatment-related organ weight, gross or histopathological findings. *Fertility effects:* there was no evidence of an effect on mating, fertility or implantation. The parental NOAEL was 250 ppm (25 mg/kg/d). The NOAEL for fertility effects was 1250 ppm (approximately 130 mg/kg/d).

N.B. The values for NOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting

A multi-generation study has been conducted in rats. In each generation the pairs were mated twice to result in, for example, litters F_{1A} and F_{1B}. The 'A' litters were sacrificed at 28 days of age, whilst the 'B' litters were mated to produce the subsequent generation. The study design included determinations of body weights, food consumption, clinical signs, oestrus cycling, mating, fertility, gestation length and litter size. Slight parental toxicity was evident in the reduced body weight gains of the F_0 males and increased relative liver weights of F_{1B} females and, to a lesser extent, F_0 parent animals. There was no evidence of an effect on mating, fertility or implantation at doses of up to 132 mg/kg/d.

5.9.1.1 Human data

No available information.

5.9.1.2 Other relevant information

No available information.

5.9.1.3 Summary and discussion of fertility

Fuberidazole did not demonstrate any adverse effects on fertility in a two-generation reproductive study in rats at doses of up to 132 mg/kg/d. Therefore, no classification for fertility effects is proposed.

Directive 67/548/EEC:	**no classification is proposed**
CLP Regulation:	**no classification is proposed**

5.9.2 Developmental toxicity

Title 7.2. Developmental toxicity studies

Dose schedule	Dose levels	Observations and remarks (effects of major toxicological significance)
Oral (gavage) Rats/FB 30 20 to 23 females/group Not guideline or GLP	0, 10, 30, 100 mg/kg/d in 0.5% aqueous 'Cremophor' emulsion Administered from gestation days 6 to	The foetuses were delivered by caesarean section on day 20 of pregnancy. *Maternal toxicity*: there were no treatment-related effects on general behaviour, body weight gain and mortality at any dose. *Developmental toxicity*: there were no embryotoxic or teratogenic effects at any dose. The NOAEL for maternal and developmental toxicity was 100 mg/kg/d.

<table>
<tr><td>(Machemer, 1975 & Eiben, 2004 in Reference 2)</td><td>15</td><td></td></tr>
<tr><td>Oral (gavage)
Rats/Wistar
25 females/ group
OECD 414
GLP
(Klaus, 2000 & Eiben, 2004 in Reference 2)</td><td>0, 1, 8, 64 mg/kg/d in 0.5% aqueous carboxymethyl-cellulose
Administered from gestation days 6 to 19</td><td>The foetuses were delivered by caesarean section on day 20 of pregnancy.
Maternal toxicity: there were no maternal mortalities. The only effects noted occurred in the high-dose group: a transient but distinct decrease in food intake on days 6 to 12 (up to 35%); distinct body weight loss after the first administration (11g, compared with a 2g gain in the controls); marginally reduced body weight gain during the gestation period (11% overall; 88% reduction over days 6 to 10); marginally decreased final body weights and corrected body weight change (reduced by 6.5% and 11.2%, respectively, compared with the controls).
Developmental toxicity: the number of foetuses recovered and their weights were unaffected by treatment. A uni/bilateral slight dilation of the renal pelvis occurred in 5% (36%), 4.7% (26%), 11.4% (55%), 9% (63%) of foetuses (litters) at 0, 1, 8 & 64 mg/kg/d (contemporary historical control range from 18 studies was 0.8-15.2% for foetuses and 10-77% for litters). The incidence of incompletely ossified 5th caudal vertebral bodies in the foetuses was increased with treatment: 60.3%, 55.6%, 61%, 79.1% at 0, 1, 8 & 64 mg/kg/d (contemporary historical control range from 21 studies was 36.7-68.95 for foetuses). The foetal incidence of wavy ribs was decreased with treatment: 14.3%, 5.3%, 6.8%, 3.0% at 0, 1, 8 & 64 mg/kg/d (contemporary historical control range from 19 studies was 2.0-14.3%). Microphthalmia occurred in 0, 1, 1, 0 animals at 0, 1, 8 & 64 mg/kg/d. Anophthalmia was not recorded in any animals.
The NOAEL for maternal and developmental toxicity was 8 mg/kg/d.</td></tr>
<tr><td>Oral (dietary)
2 generation
Rats/Wistar
25/sex/dose
OECD 416
GLP
(Holzum, 1989 in Reference 2)</td><td>0, 50, 250, 1250 ppm
Actual intakes
Males:
0, 4, 20, 103 mg/kg/d
Females:
0, 5, 25, 132 mg/kg/d
Administered from at least 105 days before mating of F_0 animals until sacrifice of the F_1 animals (at weaning of F_2)</td><td>Parental toxicity: body weight gain of the high-dose F_0 males was reduced by approximately 20% at week 4. At sacrifice this difference had reduced to about 5%. The terminal body weights of the F_{1B} adults were unaffected by treatment. The relative liver weights of the F_{1B} females were statistically significantly increased in the high-dose group (by 3%, 4%, 18% at 50, 250, 1250 ppm). Relative liver weights were also increased in the F_0 animals in response to treatment (0%, 5%, 5%, 7% in males and 0%, 0%, -3%, 12% in females at 0, 50, 250, 1250 ppm), although these changes were not always statistically significant. No histological correlates to the increased liver weight could be determined, and there were no other treatment-related organ weight, gross or histopathological findings.
Toxicity to pups: there were no treatment-related effects on organ weight or findings on gross necropsy of the pups. At birth, body weight of the pups was comparable amongst all groups. However, reduced body weight gain throughout the first 4 weeks after birth was recorded in F_2 pups (101%, 105%, 88.5% of control values at 4 weeks in the 50, 250, 1250 ppm groups). A similar effect occurred in the F_{1B} pups (92%, 99%, 87% of control values at 4 weeks in the 50, 250, 1250 ppm groups), but the body weight gains of F_{1A} pups were unaffected by treatment.
Reproductive effects: treatment was associated with reductions in the viability and lactation indices, as illustrated in the table below.
<table>
<tr><td>Dose (ppm)</td><td>Viability index</td><td>Lactation index</td><td>Viability index</td><td>Lactation index</td></tr>
<tr><td></td><td colspan="2">F_{1A} generation</td><td colspan="2">F_{1B} generation</td></tr>
<tr><td>0</td><td>97.4</td><td>87.9</td><td>97.2</td><td>92.6</td></tr>
<tr><td>50</td><td>99.1</td><td>88.2</td><td>98.2</td><td>91.2</td></tr>
<tr><td>250</td><td>98.8</td><td>92.9</td><td>95.0</td><td>80.7*</td></tr>
</table></td></tr>
</table>

		1250 94.4 87.0 94.6 75.5* **F_{2A} generation** **F_{2B} generation** **0** 95.3 66.0 90.7 31.7 **50** 82.8* 64.7 86.5 48.5* **250** 94.7 86.2* 82.1* 30.5 **1250** 80.6* 56.3 60.9* 35.8 *p < 0.01 The historical control data range for the F_{2A} generation was 78.7 to 100 (mean 95.9), whereas that for the F_{2B} generation was 88.0 to 99.5 (mean 95.2) (same laboratory, 1978-1986). The parental NOAEL was 250 ppm (25 mg/kg/d). The NOAEL for reproductive effects was 50 ppm (4 mg/kg/d).
Oral (gavage) Rabbits/ Chinchilla, 20 females/group Not guideline or GLP (Becker, 1982 & Eiben, 2004 in Reference 2)	0, 10, 30, 100 mg/kg/d in 0.5% 'Cremophor EL' (4 ml/kg/d) Administered from gestation days 6 to 18	Foetuses were examined on day 28 of pregnancy. *Maternal toxicity*: at 100 mg/kg/d, feed consumption of the dams was reduced by 22% and body weight gain was lowered during the treatment period (a loss of 1.5 g compared with a gain of 3.8 g in the controls when corrected for uterine weight). *Developmental toxicity*: at 100 mg/kg/d, the mean body weight of the foetuses was slightly reduced (by approximately 5%). There were no treatment-related malformations or any other effects. There were no incidences of microphthalmia or anophthalmia. The NOAEL for maternal toxicity was 30 mg/kg/d. The NOAELs for foetotoxicity and developmental toxicity were 30 mg/kg/d and 100 mg/kg/d, respectively.

N.B. The values for NOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting

In a developmental study in rats, in which fuberidazole was administered at up to 100 mg/kg/d, there were no indications of maternal toxicity in the limited examinations made: behaviour, physical appearance, survival and weight gain were unaffected. The substance was administered during the period of organogenesis (gestation days 6 to 15). No adverse developmental effects on external and visceral anomalies or skeletal malformations were noted.

In a further oral developmental study in rats, fuberidazole was administered at up to 64 mg/kg/d from gestation days 6 to 19. The highest dose resulted in mild to moderate maternal toxic effects (which were particularly evident during the early stages of the study), mainly manifested as reduced food consumption and reduced body weight gains. The foetuses were examined for external and visceral anomalies and for skeletal malformations and retardation. The incidence of uni/bilateral slight renal pelvis dilation was increased with treatment (statistically significant at 8 mg/kg/d), although not in a dose-dependent fashion. This effect is generally regarded as a sign of retarded intra-uterine development. However, the foetal and litter incidences of this were well within the historical control ranges. The skeletal findings were contradictory, in that exposure to fuberidazole appeared to reduce development/ossification (as demonstrated by the increased incidence of incomplete ossification of the 5^{th} caudal vertebral bodies) and yet also increase development/ossification (reduced incidence of wavy ribs). The benzimidazole fungicide benomyl is known to impair microtubule formation (Reference 7) and may produce ocular malformations by disruption of neuronal proliferation and migration. Beta-III tubulin is found almost exclusively in neurons and, with β-1 tubulin, forms the permanent microtubule skeleton of the eye. Therefore, particular attention was given to the incidences of microphthalmia and anophthalmia in this study: the occurrences of these were incidental and unaffected by treatment.

A multi-generation study has been conducted in rats (see section 5.9.1). The offspring were examined for treatment-related effects on sex ratio, pup viability, body weight gain, clinical signs and gross necropsy. Slight parental toxicity was evident in the reduced body weight gains of the F_0 males and increased relative liver weights of F_{1B} females and, to a lesser extent, F_0 parent animals.

The gestation period, male/female ratio, total numbers of pups and numbers of live births per dam were unaffected by exposure to fuberidazole. Likewise, pup weight at birth was similar between groups. However, there was a statistically significant decrease in the viability index (ratio of surviving pups to live-born pups after 5 days) in the F_2 generation. The reduction in the viability index of the F_{2B} generation showed a dose-response relationship (and was lower than the historical control data), although that in the F_{2A} generation did not. In the absence of an F_3 generation, the effect on the F_{2B} generation is considered to be a treatment-related effect that may only manifest from the F_2 generation. The decrease in the viability index was not clearly associated with reductions in the body weight gain of the pups: for example, at 250 ppm the body weight gain was greater than that of the controls, whereas the viability index was reduced. There was an association with parental toxicity (increased liver weights in the F_{1B} females), but the terminal body weights of the F_{1B} females were unaffected by treatment; therefore, the reduced viability indices of the pups could not be explained by a general poor condition of the dams. The reduced viability index in the F_{1A} 50 ppm group was considered to be a chance finding, since it did not occur in the 250 ppm group or in the 50 ppm group of the F_{1B} mating.

The lactation index (ratio of surviving pups at 4 weeks to living pups at day 5) was statistically significantly reduced in the F_{1B} generation in the mid- and high-dose groups, but this effect was not evident in the F_{1A} or F_2 generations. Again, the decrease in the lactation index was not associated with reduced terminal body weights of the F_0 dams. However, it may have been associated with the possibly reduced body weight gains during the first four weeks in the F_{1B} pups. Neither body weight gains nor lactation indices were affected by fuberidazole treatment in the F_{1A} pups, whereas the F_2 generation pups showed reduced body weight gains without an adverse effect on the lactation indices.

In a rabbit developmental study, fuberidazole was administered during the period of organogenesis (gestation days 6 to 18). The body weights, appearance and behaviour of the dams were recorded during the gestation period. The only observed maternal effects were on feed consumption and body weight gain. On day 28 the foetuses were examined for sex distribution, weight, retardation of the skeletal system and for external and internal malformations. The reduced body weights measured in the foetuses of the high-dose group were probably related to the maternal toxicity that occurred in this group. No other treatment-related effects were observed.

5.9.2.1 Human data

No available information.

5.9.2.2 Other relevant information

The available toxicokinetic data did not indicate whether or not fuberidazole is likely to be excreted in breast milk.

5.9.2.3 Summary and discussion of developmental toxicity

In one oral developmental study in rats and one in rabbits, no developmental toxicity was noted. In a second rat developmental study, the skeletal findings were contradictory but only occurred in conjunction with maternal toxicity. A reduction in ossification in rodents is associated with maternal toxicity, and wavy ribs are a well-recognised common variation. As the effects observed were minor, non-specific and secondary to maternal toxicity, it is concluded that the classification criteria of Directive 67/548/EEC and the CLP Regulation were not met based on these findings.

A possible developmental effect occurred when fuberidazole was administered to rats in a two-generation study. A reduced viability index was observed in F_{2B} pups in the absence of overt maternal toxicity and changes in the pup weights. It did not occur in the F1 pups.

Because of this effect it should be considered if classification for fertility effects may be appropriate. As there is no evidence that fuberidazole causes developmental toxicity in humans, Category 1 (in accordance with the criteria in Directive 67/548/EEC) is not appropriate. Likewise, Category 2 is not appropriate because there is not clear evidence of adverse effects in one or more species. Category 3 may be appropriate; however, the findings were inconsistent between different matings in the same generation, in that a dose-response relationship occurred in the F_{2B} pups but not in the F_{2A} pups. Additionally, although the viability index was reduced in both of the F_2 high-dose litters, the reduction in the F_{2A} litter was relatively small (15% less than the control value) and within the historical control data range. Therefore, given the relatively small adverse effects and their inconsistent nature, it is concluded that the criteria for classification for developmental effects are not met under either Directive 67/548/EEC or the CLP Regulation.

Directive 67/548/EEC:	**no classification is proposed**
CLP Regulation:	**no classification is proposed**

5.10 Other effects

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 PHYSICOCHEMICAL PROPERTIES

6.1 Explosivity

The explosive properties of fuberidazole (technical active substance, 96.9% purity) were investigated in accordance with EEC method A.14. The test substance did not show sensitivity to heat, shock or friction in this test Reference 8.

No classification is proposed.

6.2 Flammability

The flammability of fuberidazole (technical active substance, 96.9% purity) was assessed according to EEC methods A.10 and A.12. The test substance was not highly flammable and did not liberate gases in hazardous amounts (Reference 8).

When tested according to EEC method A.16, fuberidazole did not undergo spontaneous combustion (Reference 8).

No classification is proposed.

6.3 Oxidising potential

The oxidising properties of fuberidazole (technical active substance, 96.9% purity) were assessed according to EEC method A.17. The comparative burning rates for the test material and reference mixtures are shown in table 6.3. As the test was not conducted under an inert atmosphere or with an inert matrix, the result could have been a false positive. It was therefore repeated with the inclusion of an inert material (diatomite); the results of this test confirmed that fuberidazole does not have oxidising properties when tested in line with this method (Reference 8).

No classification is proposed.

Table 6.3. Comparative burning rates for test and reference mixtures

	Mixture	**Burning rate**
Test 1	60% fuberidazole / 40% cellulose	1.30 mm/s
	60% barium nitrate / 40% cellulose	1.10 mm/s
Test 2	60% fuberidazole / 40% cellulose	0.99 mm/s
	60% barium nitrate / 40% celluluse	1.27 mm/s
	70% fuberidazole / 30% diatomite	1.50 mm/s

7 ENVIRONMENTAL HAZARD ASSESSMENT

Fuberidazole is a systemic agricultural fungicide.

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

Based on the aquatic photolysis study, fuberidazole has the potential to undergo significant photodegradation. Whilst the acute toxicity to fish studies were undertaken in the absence of light, exposure solutions during the algal growth inhibition study and acute toxicity to *Daphnia magna* study were subjected to light. Limited losses were observed indicating rapid photodegradation did not occur. This may reflect differences between study conditions including light intensity, pH and presence of dissolved salts.

No relevant water degradation products were observed in the water-sediment degradation study and limited water photodegradation products are expected in the environment. On this basis, ecotoxicity

studies with water degradation products were note undertaken. In addition, aquatic sediment degradation products were observed at insufficient concentrations to require further ecotoxicity testing.

7.1.1.1 Fish

- Short term toxicity to fish

Two static 96-hour acute toxicity to fish studies are available following OECD Guideline 203 using *Oncorhynchus mykiss* (rainbow trout) and *Lepomis macrochirus* (bluegill sunfish). Test material was dissolved in DMF (Dimethylformamide) solvent to aid dispersion (within permitted guideline concentrations) and the studies were conducted in the dark to avoid photodegradation. No adverse effects or mortality was observed in either controls or solvent controls.

Oncorhynchus mykiss
Fuberidazole was generally stable under the tests conditions with analytical concentrations 86 – 103 % of nominal for all but the lowest exposure concentration. At the lowest concentration (0.31 mg/l nominal), measured concentrations were 73 – 98% of nominal. Results were based on mean measured concentrations. The 96-h LC_{50} for *Oncorhynchus mykiss* (Reference 10) was 0.91 mg a.s./l with 95% confidence intervals of 0.70-1.2 mg a.s./l.

Lepomis macrochirus (Reference 10)
Fuberidazole was stable under test conditions with analytical concentrations 95 -103 % of nominal. Results were based on mean measured concentrations. The 96-h LC_{50} was 4.3 mg a.s./l with 95% confidence intervals of 2.8-6.5 mg a.s./l.

- Long-term toxicity to fish

No studies are available.

7.1.1.2 Aquatic invertebrates

- Short term toxicity to aquatic invertebrates

Following OECD Guideline 202, the acute toxicity to the water flea (*Daphnia magna*) was assessed under semi-static conditions (Reference 9). The study was run using a test system 16:8 hour light-dark cycle. Measured concentrations were ≥80 % of nominal and results were based on nominal concentrations the 48-h EC_{50} was 4.7 mg a.s./l with 95% confidence intervals of 3.7-6.1 mg a.s./l.

- Long term toxicity to aquatic invertebrates

A semi-static 21-day long-term *Daphnia magna* toxicity study following OECD Guideline 211 is available (Reference 10). Measured concentrations were significantly <80% of nominal and results are based on measured concentrations. The 21 day NOEC based on mean number of offspring was 0.12 mg a.s./l based on measured data.

7.1.1.3 Algae and aquatic plants

A static algal growth inhibition study is available using *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) and following OECD Guideline 201 (Reference 10). Test material was dissolved in DMF (Dimethylformamide) solvent to aid dispersion (within permitted guideline concentration). Test vessels were illuminated at ~8600 lux using fluorescent tubes. All validation criteria were met. Analytical measurement of fuberidazole was undertaken at 0 hours and 96 hours using samples without algae. Measured concentrations at 0 hours were 89 to 97 % of nominal. Measured concentrations at 96 hours were 76 – 87 % of nominal. Whilst losses were observed (most likely due to photodegradation) study results were based on nominal concentrations; 72 h E_rC_{50} 12.1 mg a.s./l with 95 % confidence interval of 7.7-23.4 mg a.s./l; and, $NOEC_{50}$ 0.5 mg a.s./l. As recalculating the results based on measured data would not produce a revised E_rC_{50} below the current $L(E)C_{50}$ of 0.91 mg a.s./l for fish based on measured data, a revised E_rC_{50} is not included here for the purpose of classification and labelling.

7.1.1.4 Sediment organisms

No studies are available.

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.

7.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

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

Fuberidazole is considered hydrolytically stable under environmentally relevant pH and temperature conditions. It is susceptible to photodegradation in the environment. However, fuberidazole rapidly dissipates from water by rapid partitioning to sediment where it has a longer residence time. Under

environmentally relevant conditions, where suspended solids are likely and light penetration limited (especially at different times of the year in different EU locations), significant environmental photodegradation is considered unlikely before partitioning to sediment. Once partitioned to the sediment phase, photodegradation is unlikely to be an important degradation pathway. Considering this and levels of mineralisation in the simulation study, fuberidazole is not considered to undergo rapid and ultimate degradation under environmental conditions and is considered not readily degradable (<70 % mineralisation in the aquatic environment within 28 days) for the purpose of classification and labelling.

In addition, fuberidazole was not observed to undergo rapid photodegradation during ecotoxicity studies undertaken in the presence of light. This may reflect differences in light intensity, pH and dissolved salts, the parameters used in the ecotoxicity testing.

The $\log K_{ow}$ of fuberidazole increases with increasing pH. The highest measured $\log K_{ow}$ value of 2.79 at pH 9 is less than 3 indicating a low bioaccumulation potential. Also a BCF estimate indicates a low BCF_{fish} of 46.9. On this basis a fish aquatic bioaccumulation study has not been conducted.

Fuberidazole exhibited less acute toxicity to algae and aquatic invertebrates compared to fish. The lowest acute toxicity value was 96-h LC_{50} 0.91 mg a.s./l for *Oncorhynchus mykiss*. The study was performed according to GLP and standard test guidelines and all validation criteria were met. The species is considered a representative aquatic species for the fish trophic level and appears to be more sensitive than other fish species, invertebrates and algae. In summary, the study is acceptable for the purpose of classification under Directive 67/548/EEC and the CLP Regulation since a suitable test method and representative aquatic species were used.

Given that limited water degradants are anticipated in the environment, there are no ecotoxicity data pertaining to fuberidazole degradation products.

Following Directive 67/548/EEC, fuberidazole should be classified Dangerous for the Environment with the following risk and safety phrases:
N Dangerous for the Environment
R50 Very toxic to aquatic organisms
R53 May cause long term effects in the environment
S60 This material and its container must be disposed of as hazardous waste
S61 Avoid release to the environment. Refer to special instructions/Safety Data Sheet

The following Special Concentration Limits should apply:

Classification of the preparation		
N, R50-53	N, R51-53	R52-53
Cn ≥ 25%	2.5% ≤ Cn <25%	0.25% ≤ Cn <2.5%

Where Cn is the concentration of fuberidazole in the preparation.

Based on the CLP Regulation, fuberidazole should be classified
Aquatic Acute 1, Aquatic Chronic 1
With the following labelling: H400 'Very toxic to aquatic life' and H410 'Very toxic to aquatic life with long lasting effects'
Signal Word: 'Warning' and environmental warning label.

An M factor of 1 is applicable based on $0.1<L(E)C_{50}\leq 1$ mg/l.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Fuberidazole is a benzimidazole fungicide that is used as a seed treatment. In 2008 it was approved for Annex I listing as a 3A Review compound under Council Directive 91/414/EEC, with the UK as Rapporteur Member State. In accordance with Article 36(2) of the CLP Regulation, fuberidazole should now be considered for harmonised classification and labelling. Therefore, this proposal considers all human health and environmental end points.

OTHER INFORMATION

This substance has been reviewed under Council Directive 91/414/EEC, with the rapporteur Member State being the United Kingdom. The studies evaluated in this dossier were taken from the draft assessment report produced under this review programme; where necessary, the full study reports were consulted, but these are generally not publicly available. Where other information from additional references has been sourced, this is indicated. A literature search did not reveal any additional information on the human health impact of fuberidazole.

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