CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: TRIADIMENOL

EC Number:	259-537-6
CAS Number:	55219-65-3
Index Number:	Not allocated
Contact details for dossier submitter:	UK REACH Competent Authority, Chemicals Regulation Directorate, Health and Safety Executive, United Kingdom.

Version number: **2** **Date:** **June 2011**

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Triadimenol***
EC number:	***259-537-6***
CAS number:	***55219-65-3***
Annex VI Index number:	***Not allocated***
Degree of purity:	***The minimum purity is 97 %. This comprises A-isomer (threo) 78 to 88 %, B-isomer (erythro) 12 to 22%.***
Impurities:	***The manufacturer has requested that the impurities remain confidential. According to the present specification of industrially-produced triadimenol, all impurities are individually present at ≤ 1 %.***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Not listed	Not listed
Current proposal for consideration by RAC	Acute Tox 4; H302 Repr Cat 2; H361f Aquatic chronic 2; H411	Xn; R22 Repro. Cat. 3; R62 R52/53
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox 4; H302 Repr Cat 2; H361f Aquatic chronic 2; H411	Xn; R22 Repro. Cat. 3; R62 R52/53

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				Conclusive but not sufficient for classification
2.2.	Flammable gases				Data lacking
2.3.	Flammable aerosols				Data lacking
2.4.	Oxidising gases				Data lacking
2.5.	Gases under pressure				Data lacking
2.6.	Flammable liquids				Data lacking
2.7.	Flammable solids				Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures				Conclusive but not sufficient for classification
2.9.	Pyrophoric liquids				Data lacking
2.10.	Pyrophoric solids				Data lacking
2.11.	Self-heating substances and mixtures				Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases				Data lacking
2.13.	Oxidising liquids				Data lacking
2.14.	Oxidising solids				Conclusive but not sufficient for classification
2.15.	Organic peroxides				Data lacking
2.16.	Substance and mixtures corrosive to metals				Data lacking
3.1.	Acute toxicity - oral	Acute Tox 4; H302			
	Acute toxicity - dermal				Conclusive but not sufficient for classification
	Acute toxicity - inhalation				Conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation				Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation				Conclusive but not sufficient for

					classification
3.4.	Respiratory sensitisation				Data lacking
3.4.	Skin sensitisation				Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity				Conclusive but not sufficient for classification
3.6.	Carcinogenicity				Conclusive but not sufficient for classification
3.7.	Reproductive toxicity	**Repr Cat 2; H361f**			
3.8.	Specific target organ toxicity –single exposure				Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure				Conclusive but not sufficient for classification
3.10.	Aspiration hazard				Data lacking
4.1.	Hazardous to the aquatic environment	**Aquatic chronic 2; H411**			
5.1.	Hazardous to the ozone layer				Data lacking

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Warning
Hazard statements: H302, H361f, H411
Precautionary statements: Not required as PS are not included in Annex VI.

Proposed notes assigned to an entry:

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness				Conclusive but not sufficient for classification
Oxidising properties				Conclusive but not sufficient for classification
Flammability				Conclusive but not sufficient for classification
Other physico-chemical properties				Conclusive but not sufficient for classification
Thermal stability				Conclusive but not sufficient for classification
Acute toxicity	Xn; R22			
Acute toxicity – irreversible damage after single exposure				Conclusive but not sufficient for classification
Repeated dose toxicity				Conclusive but not sufficient for classification
Irritation / Corrosion				Conclusive but not sufficient for classification
Sensitisation				Conclusive but not sufficient for classification
Carcinogenicity				Conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity				Conclusive but not sufficient for classification
Toxicity to reproduction – fertility	**Repr. Cat. 3; R62**			
Toxicity to reproduction – development				Conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation				Conclusive but not sufficient for classification
Environment	**R52/53**			

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: Xn
R-phrases: 22-62-52/53
S-phrases: (2)-(13)-36-37-(46)-61

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Triadimenol has not previously been reviewed for harmonised classification and labelling.

2.2 Short summary of the scientific justification for the CLH proposal

Triadimenol is a triazole systemic fungicide that is used as a seed treatment and a foliar spray. In 2008, it was approved for Annex I listing as a 3 A review substance under Council Directive 91/414/EEC, with the UK as Rapporteur Member State. In accordance with Article 36 (2) of the CLP Regulation, triadimenol should now be considered for harmonised classification and labelling. Therefore, this proposal considers all human health and environmental end points. This CLH dossier presents a classification and labelling proposal based mainly on the information presented in the assessment of triadimenol under Directive 91/414/EEC, although some of the acute toxicity studies were submitted after that assessment. The assessment made under that Directive is attached to the IUCLID 5 dossier. At the time of writing, no REACH registration dossiers had been submitted for this substance.

Triadimenol is a mixture of two diastereomers, isomer A (threo-configuration, *RS*- and *SR*-form) and isomer B (erythro-configuration, *SS*- and *RR*-form). Isomer A has a higher level of biological activity than isomer B. Each isomer is in itself a racemic mixture of two optical isomer forms. The ratio of the two isomers in the currently manufactured material is ≈ 80 % isomer A: ≈ 20 % isomer B (hereafter referred to as 80:20 material). During the development of triadimenol in the 1970s, material was produced on a laboratory scale with an approximate A:B ratio of 60:40. In the 1980s and beyond, the 80:20 material was produced. Information on the test material's specification is presented as far as possible, but was not always stated in the study reports.

Test materials with varying purities were used in the toxicology studies. The current minimum purity is 97 %, which is similar to or more pure than the material used in the majority of studies. During the evaluation under Directive 91/414/EEC, it was concluded that the data provided a worst-case scenario with respect to impurities. It was also concluded that the profile of impurities present in the older material was almost identical to those in the current specification.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Not currently listed on Annex I of the CLP Regulation.

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Not currently listed on Annex I of the CLP Regulation.

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

The manufacturer currently applies the Directive 67/548/EEC classification criteria, but if the CLP criteria were applied the equivalent self-classification would be Acute Tox 4; H302, Aquatic Chronic 2; H411.

2.4.2 Current self-classification and labelling based on DSD criteria

Xn;

R22,

R52-53.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

In 2008, Triadimenol was approved for Annex I listing as a 3 A review substance under Council Directive 91/414/EEC, with the UK as Rapporteur Member State. In accordance with Article 36 (2) of the CLP Regulation, triadimenol should now be considered for harmonised classification and labelling. Therefore, this proposal considers all human health and environmental end points.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

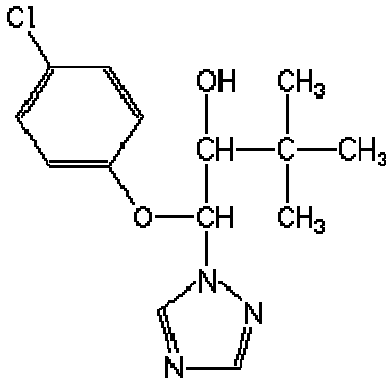
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	259-537-6
EC name:	α-tert-butyl-β-(4-chlorophenoxy)-1H-1,2,4-triazole-1-ethanol
CAS number (EC inventory):	
CAS number:	55219-65-3
CAS name:	1H-1,2,4-triazole-1-ethanol, .beta.-(4-chlorophenoxy)-.alpha.-(1,1-dimethylethyl)-
IUPAC name:	1-(4-chlorophenoxy)-3,3-dimethyl-1-[1H-1,2,4]triazol-1-yl-butan-2-ol
CLP Annex VI Index number:	Not allocated
Molecular formula:	C_{14} H_{18} Cl N_3 O_2
Molecular weight range:	295.8 g/mol

Structural formula:



1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Triadimenol	≥ 97 %	97 to 100 %	

Current Annex VI entry: Not listed

Triadimenol is a mixture of two diastereomers, isomer A (threo-configuration, *RS*- and *SR*-form) and isomer B (erythro-configuration, *SS*- and *RR*-form). Each isomer is in itself a racemic mixture of two optical isomer forms. The ratio of the two isomers in the currently manufactured material is ≈ 80 % isomer A: ≈ 20 % isomer B (hereafter referred to as 80:20 material). Further details on the composition are provided in the technical dossier.

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
All impurities are confidential		Process impurities are individually present in the range of 0 to 1 %	

Current Annex VI entry: Some of the impurities are listed on Annex VI. These impurities were thoroughly evaluated during the review under Directive 91/414/EEC and do not impact on the classification proposed in this dossier.

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
None				

Current Annex VI entry: Not applicable

1.2.1 Composition of test material

During the development of triadimenol in the 1970s, material was produced on a laboratory scale with an approximate A:B ratio of 60:40. In the 1980s and beyond, the 80:20 material was produced. Information on the test material's specification is presented as far as possible, but was not always stated in the study reports.

Test materials with varying purities were used in the toxicology studies. The current minimum purity is 97 %, which is similar to or more pure than the material used in the majority of studies. During the evaluation under Directive 91/414/EEC, it was concluded that the data provided a worst-case scenario with respect to impurities. It was also concluded that the profile of impurities present in the older material was almost identical to those in the current specification.

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	Pure: colourless crystals As manufactured: white to grey powder		Visual inspection
Melting point	Isomer A: 138.2ºC Isomer B: 133.5ºC	Dörr, 1979	Measured, OECD 102 DTA
Boiling point	Mixture of *SR* and *SS* or *RR*: 155 to 270ºC	Klusacek & Krasemann, 1986	Measured, OECD 113
Relative density	Isomer A: 1.237 at 22ºC Isomer B: 1.299 at 22ºC	Weber, 1987a; Weber, 1987b	Measured, OECD 109
Vapour pressure	Isomer A (*SR*): $6x10^{-7}$ Pa at 20ºC; $1x10^{-6}$ at 25ºC (extrapolated) Isomer B (*SS* and *RR*): $4x10^{-7}$ Pa at 20ºC; $9x10^{-7}$ at 25ºC (extrapolated)	Weber & Krohn, 1996	Measured, OECD 104
Surface tension	Mixture of *SR* and *SS* or *RR: 54.4* mN/m at 20ºC and 130 mg/L	Krohn, 1999	Measured, EEC method A 5
Water solubility	Isomer A: 0.049 g/L at 20ºC Isomer B: 0.095 g/L at 20ºC As it is a very weak base that can only be completely protonized in non-aqueous systems in the presence of very strong acids, water solubility in the acidic and alkaline pH range was not determined	Leimkuehler, 1980	Measured, OECD 105 (Flask)
Partition coefficient n-octanol/water (log value)	Isomer A: 3.08 at 25ºC Isomer B: 3.28 at 25ºC The effect of pH was not investigated	Krohn, 1984	Measured, OECD 107 (Shake flask)
Flash point	Not applicable (melting point above 40ºC)		
Flammability	Not highly flammable and does not liberate gases in hazardous amounts	Eberz, 1999	Measured, EEC A 10 and 12
Explosive properties	Not explosive	Eberz, 1999	Measured, EEC A 14
Self-ignition temperature	Does not spontaneously combust	Eberz, 1999	Measured, EC A.16
Oxidising properties	No oxidising properties	Eberz, 1999	Measured, EEC A 17
Granulometry			

Stability in organic solvents and identity of relevant degradation products			
Dissociation constant	No dissociation occurred		Measured, OECD 112
Viscosity			

2 MANUFACTURE AND USES

2.1 Manufacture

Information on the manufacture of triadimenol is confidential.

2.2 Identified uses

Triadimenol is used as a fungicidal seed and foliar spray treatment in agricultural applications.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
Refer to table 9			

3.1 Physico-chemical properties

3.1.1 Summary and discussion

Refer to table 9.

3.1.2 Comparison with criteria

Refer to table 9.

3.1.3 Conclusions on classification and labelling

Triadimenol does not meet the criteria for classification.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

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

4.1.1 Non-human information

The toxicokinetics and metabolism of triadimenol have been investigated in the rat. The active substance was rapidly and extensively (almost 100%) absorbed following oral administration of low (1 mg/kg/d) and high (100 mg/kg/d) doses. Peak concentrations were achieved in most organs and tissues within one hour, with the highest peak concentrations occurring in fat, the urinary bladder and the liver. Excretion was also extensive and was mainly via the faeces in males (> 90 % of the administered dose in the bile) and via both faeces and bile in females. At 24 hours after administration of single or repeated doses, total excretion was 80-90% in males and females; as excretion was not complete by 24 hours, accumulation of triadimenol may occur. By 120 hours, excretion had reached almost 100%. The half-life of elimination from plasma was between 6.4 and

9 hours after single or repeated (for 14 days) administrations. Retention in tissues was very limited, with residues in the body (excluding the gastrointestinal tract) being up to 0.06% of the administered dose after single low (1 mg/kg/d, determined in males and females) or high (100 mg/kg/d in males) doses and after a repeated low-dose administration (males only; residues determined at 120 hours). After a single dose, the highest residues (determined in male rats) were found in fat, the bladder and the liver; amounts of radioactivity were below the limit of detection by 72 hours after administration of the dose. The results indicated that enterohepatic recirculation occurred. Triadimenol was rapidly metabolised, predominantly by hydroxylation to triadimenol-hydroxy then further oxidation to triadimenol-carboxy. Oxidation of the secondary hydroxy group to form metabolites related to triadimefon was indicated at low levels (< 2 %), but triadimefon itself was not identified. Differences between the metabolites formed from different dose levels and the sexes were minor.

4.1.2 Human information

No available information.

4.1.3 Summary and discussion of toxicokinetics

See section 4.1.1.

4.2 Acute toxicity

Acute toxicity has been investigated by the oral, inhalation and dermal routes in rats and mice. There is also limited information on intra-peritoneal and sub-cutaneous administration in these species.

Table 11: Summary table of relevant acute toxicity studies*

Method	LD_{50}	Remarks	Reference
Oral Rats/Wistar, 3 females/group, repeated (total of 6 animals tested) 2000 mg/kg in 2% Cremophor EL 14-day observation period 80:20 mixture, purity 97.2% OECD 423 (acute toxic class), GLP	> 2000 mg/kg	Animals were fasted for 16-24 hours prior to administration of the test substance. In the first test at 2000 mg/kg, no animals died. In the repeat of the test with this dose, one animal died on day 3. Clinical signs, which appeared between 2 and 11 days after dosing, included piloerection, increased motility, uncoordinated gait, spasmodic state, aggression, hunched posture, laboured breathing. Gross necropsy did not show any treatment-related findings.	Schüngel, 2005c
Oral Rats/Wistar, 15/sex/group 250-1500 mg/kg in water/Cremophor EL 14-day observation period 80:20 mixture, purity 92.7% Not guideline or GLP	720 mg/kg (fasted animals) 1068 mg/kg (unfasted animals)	Two investigations were performed: in one, rats were fed normally; in the other, they were fasted for 16 hours prior to dosing. Deaths occurred from day 1 in fasted and unfasted animals. Clinical symptoms were consistent with effects on the CNS and included lethargy, piloerection, laboured breathing. Severe behavioural disturbances (aggression, self-mutilation) were noted. Gross necropsy of animals that died showed signs of irritation of mucous membranes of the gastrointestinal tract, which were present to a lesser degree in unfasted animals.	Mihail & Thyssen, 1980
Inhalation Rats/Wistar, 10/sex/group 1 hour exposure: 0.31, 0.67, 1.56 mg/L 4 hours' exposure: 0.088, 0.31, 0.95 mg/L Nose-only exposure 14-day observation period 80:20 mixture, purity 92.7% Not guideline or GLP	> 0.95 mg/L	Test atmosphere concentration was determined by analysis. Particle size analysis was not performed. The highest concentrations tested in each of the 1-hour and 4-hour exposures were stated to be the maximum attainable. There were no deaths, clinical signs, effects on body weight or abnormal gross necropsy findings following a single 1-hour exposure. Following a single 4-hour exposure, one female in the 0.31 mg/L group died on day 14, without having shown any previous symptoms. The study authors attributed this death to acute pneumonic bacterial disease. There were no other deaths or treatment-related gross necropsy findings.	Mihail & Thyssen, 1980
Dermal Rats/Wistar, 5/sex/group 2000 mg/kg applied under a semi-occlusive dressing for 24 hours 14-day observation period 80:20 mixture, purity 97.2% OECD 402, GLP	> 2000 mg/kg (males and females)	There were no deaths, clinical signs, effects on body weight or gross pathology.	Schüngel, 2005b
Dermal	> 5000 mg/kg	There were no deaths, clinical signs of toxicity or abnormal gross necropsy findings.	Mihail & Thyssen,

Rats/Wistar, 5/sex/group 2500 & 5000 mg/kg applied for 24 hours (dressing unspecified) 14-day observation period 80:20 mixture, purity 92.7% Not guideline or GLP			1980

**The studies included in this table are regarded as the key studies for classification purposes. Additional studies can be found in the pesticide evaluation report conducted under Directive 91/414/EEC; however, in the opinion of the dossier submitter, these do not impact the classification decision.*

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Two acute oral toxicity studies have been conducted on triadimenol. LD_{50} values of 720 (fasted rats), 1068 (unfasted rats) and > 2000 mg/kg (fasted rats) were obtained.

4.2.1.2 Acute toxicity: inhalation

One acute inhalation toxicity study has been conducted, in which the maximum attainable concentration was used. An LC_{50} of > 0.95 mg/L was obtained.

4.2.1.3 Acute toxicity: dermal

LD_{50} values of > 2000 and > 5000 mg/kg were obtained in two acute dermal studies.

4.2.1.4 Acute toxicity: other routes

Not relevant for classification.

4.2.2 Human information

No information available.

4.2.3 Comparison with criteria

A range of LD50 values, from 720 mg/kg to > 2000 mg/kg, were obtained from acute oral toxicity studies. The cut-off for classification for acute toxicity category 4 in the CLP Regulation (2000 mg/kg) falls within this range of values. There is no obvious explanation why the studies gave such different LD50 values: there were no major differences in the experimental animals used; the administered formulation was comparable; and there was not a marked difference in the purity/impurity profiles of the tested materials. As there are no data to indicate that the Schüngel, 2005c data should be given preference over the older LD_{50} values, it is proposed to classify for acute oral toxicity.

In an acute inhalation study, the maximum attainable concentration of 0.95 mg/L triadimenol did not result in any deaths or clinical signs of toxicity. No classification is proposed for acute inhalation toxicity.

The LD_{50} values obtained from two acute dermal studies were above the classification cut-off (≤ 2000 mg/kg) in the CLP Regulation and Directive 67/548/EEC. No classification is proposed for acute dermal toxicity.

4.2.4 Conclusions on classification and labelling

CLP Regulation:	**Acute Tox 4; H302**
Directive 67/548/EEC:	**Xn; R22**

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

The information gained from the acute toxicity studies (section 4.2) did not indicate that triadimenol resulted in toxicity to specific organs (other than the CNS) after a single exposure.

In addition to these acute toxicity studies, information on specific target organ toxicity – single exposure is available from two acute neurotoxicity studies.

Table 12. Summary of acute neurotoxicity studies

Method	Results and remarks	Reference
Oral (gavage) Mice/CFW1/males and rats/WISW/males, 3 to 10 animals/group Doses between 3 & 60 mg/kg in polyethylene glycol 400 Test material presumed to be 80:20 mixture; purity 98% Not guideline, not GLP	Pilot study (not a comprehensive evaluation of neurotoxicity) in which six pharmacological tests were conducted to establish if triadimenol had a stimulating effect on the CNS. The findings were that triadimenol: potentiated hexobarbital 'sleeping time' (anaesthesia) of mice; had a statistically significant stimulating effect on spontaneous motility of mice, which was less potent than with caffeine; resulted in effects consistent with stimulation of the CNS in mice (less potent than caffeine); had a stimulating effect on motor activity, rearing, licking/sniffing and grooming in rats; increased motor activity in mice (less potent than caffeine); transiently antagonised the ptosis and inhibition of spontaneous motility that was induced by pre-treatment with reserpine in mice (less potent than caffeine).	Polacek, 1983
Oral (gavage) Rats/Long Evans, 8-12 males/group 50, 100, 200, 400 mg/kg Presumed to be 80:20 mixture, purity not stated Guideline and GLP status not reported	To determine if the hyperactivity in rats associated with triadimefon administration was characteristic of other triazole compounds, 14 triazoles and structurally-related substances were tested, including triadimenol. Triadimenol induced hyperactivity in all dose groups.	Crofton, 1996

From the acute toxicity studies (section 4.2), there were some signs that were indicative of triadimenol having an effect on the CNS (increased motility, behavioural changes, drowsiness and lethargy). Additional information was obtained from acute neurotoxicity investigations in rats.

In a pilot study that comprised a number of tests, triadimenol at doses of 3 mg/kg and above demonstrated a stimulating effect on the CNS, which, however, was less potent than that of caffeine in the tests in which there was a comparison. The study authors surmised that the potentiation of hexobarbital anaesthesia was more likely to be a peripheral effect on the liver, such as an inhibition of barbiturate metabolism, than an effect on the CNS.

According to Crofton, 1996), it has been proposed that the hyperactivity induced by triazoles, of which triadimenol is a member, is related to altered monoamine metabolism (decreased synaptosomal dopamine reuptake); triadimenol decreases dopamine uptake in *in vitro* brain synaptosomal preparations. Crofton concluded that the crucial site in structure-activity relationship considerations of these CNS effects of triazoles is the ether oxygen, which is present in triadimenol.

4.3.2 Comparison with criteria

Triadimenol resulted in effects on the CNS in acute neurotoxicity studies. There is no indication that, at higher doses of the substance, these effects would lead to death of the animals (in an acute toxic class method test, the cut-off was 2500 mg/kg), and so a classification for STOT-SE should be considered.

STOT-SE is divided into three categories. Categories 1 and 2 are assigned on the basis of significant or severe toxicity and their criteria include guidance cut-off values.

STOT-SE 3 is reserved for transient target organ effects, which are limited to respiratory tract irritation and narcotic effects. Although triadimenol had a transient effect on the CNS, this was stimulant as opposed to narcotic, and so STOT-SE 3 would not be appropriate.

In consideration of categories 1 and 2, triadimenol induced functional disturbance that was not associated with morphological changes: there was no neuropathy or other adverse findings at histopathology. The effects were possibly mediated through a pharmacological effect rather than damage to the CNS; the transient nature of the effects would support this hypothesis. An additional consideration is triadimenol's potency in the neurotoxicity tests, which was less than that of caffeine. For these reasons, it is decided not to propose a classification for STOT-SE.

4.3.3 Conclusions on classification and labelling

CLP Regulation:	**No classification**

4.4 Irritation

4.4.1 Skin irritation

The potential of triadimenol to cause skin irritation has been tested in rabbits and humans.

Table 13: Summary table of relevant skin irritation studies*

Method	Results	Remarks	Reference
Rabbit/albino, 3 females 80:20 mixture, purity 97.2% OECD 404, GLP	Draize scores were 0 for all animals at all time points.	Not irritant	Schüngel, 2005a
Rabbit/New Zealand White, 3 females 80:20 mixture, purity 95.8% OECD 404, GLP	The Draize scores were 0 in all animals at all time points up to and including 14 days.	Not irritant	Krötlinger, 1993
Rabbits, New Zealand White, 6 animals 24 hour exposure on intact and abraded skin 80:20 mixture, purity 92.7% Not guideline or GLP	*Intact skin:* 1/6 animals had grade 1 erythema at 24 and 72 hours, and grade 1 oedema at 24 hours. All other animals scored 0. *Abraded skin*: 4/6 animals had grade 1 erythema, 1/6 animals had oedema (grade and time points of these observations not recorded).	Not irritant	Mihail & Thyssen, 1980
Rabbits/albino/6 males 80:20 mixture, purity 97.5% Similar to OECD 404, not GLP	Draize scores were 0 for all animals at all time points.	Not irritant	Nagashima, 1982a

**The studies included in this table are regarded as the key studies for classification purposes. Additional studies can be found in the pesticide evaluation report conducted under Directive 91/414/EEC; however, in the opinion of the dossier submitter, these do not impact the classification decision.*

4.4.1.1 Non-human information

Triadimenol did not cause skin irritation in two well-conducted studies in rabbits. Supportive evidence was provided by additional, non-standard, studies in rabbits.

4.4.1.2 Human information

No information.

4.4.1.3 Comparison with criteria

Several studies in rabbits gave no indication that triadimenol causes skin irritation. Triadimenol did not meet the criteria for classification as a skin irritant under the CLP Regulation or Directive 67/548/EEC.

4.4.1.4 Conclusions on classification and labelling

CLP Regulation:	**No classification**
Directive 67/548/EEC:	**No classification**

4.4.2 Eye irritation

Triadimenol's potential to cause eye irritation has been assessed in rabbits.

Table 14: Summary table of relevant eye irritation studies*

Method	Results	Remarks	Reference
Rabbits/albino/3 females 80:20 mixture, 97.2% OECD 405, GLP	All scores were 0 apart from redness of the conjunctiva, which gave mean scores of 0.3, 0.7 and 0.3 in the three animals, respectively. This effect was reversible within 3 days.	Slightly irritant	Schüngel, 2005d
Rabbits/New Zealand White, 3 females 80:20 mixture, purity 95.8% OECD guideline 405, GLP	Only effects on the conjunctiva were observed. The mean scores for conjunctival redness were 0.3, 0 and 0.3, with full resolution by 48 hours. Grade 1 chemosis occurred in 3/3 animals at 1 hour but had fully resolved by 24 hours (mean score 0 for each animal).	Slightly irritant	Krötlinger, 1993
Rabbits/New Zealand White, 8 animals 80:20 mixture, purity 92.7% Not guideline or GLP	*5 minutes' exposure* All scores were 0 apart from grade 1 conjunctival redness in 5/5 animals from 5 minutes; fully resolved in all animals by 48 hours. *24 hours' exposure* All scores were 0 apart from grade 1 conjunctival redness in 3/3 animals; fully resolved by 24 hours.	Slightly irritant	Mihail & Thyssen, 1980
Rabbits/albino, 9 males 80:20 mixture, purity 97.5% Not guideline or GLP	*Washed eyes* Grade 1 conjunctival effects in 3/3 animals at 1 to 4 hours only. *Unwashed eyes* Grade 1 corneal effects in 4/6 animals, reversible by 72 hours. Grade 1 or 2 conjunctival redness or chemosis in 6/6 animals, reversible by 96 hours.	Slightly irritant	Nagashima, 1982b

**The studies included in this table are regarded as the key studies for classification purposes. An additional study can be found in the pesticide evaluation report conducted under Directive 91/414/EEC; however, in the opinion of the dossier submitter, these do not impact the classification decision.*

4.4.2.1 Non-human information

Several studies in rabbits have consistently shown that triadimenol has only a mild irritant effect on the eyes.

4.4.2.2 Human information

No available information.

4.4.2.3 Comparison with criteria

The main effect observed was conjunctival redness, with occasional conjunctival chemosis. Since all effects were fully reversible before 21 days, Category 1 (irreversible eye effects) according to CLP (R41 in Directive 67/548/EEC) is not appropriate. The grades of conjunctival effects (mean scores of ≤ 0.7 in the guideline-compliant studies, individual scores of generally 1 in the non-guideline compliant studies) did not meet the criteria for classification as Category 2 (irritating to

eyes) in the CLP Regulation (mean scores of ≥ 2 in at least 2 of 3 animals for conjunctival redness or chemosis). The criteria for classification as R36 in Directive 67/548/EEC were also not met (conjunctival mean scores of ≥ 2.5 for redness or ≥ 2 for chemosis).

4.4.2.4 Conclusions on classification and labelling

CLP Regulation:	**No classification**
Directive 67/548/EEC:	**No classification**

4.4.4 Respiratory tract irritation

No evidence of respiratory tract irritation was found in one acute inhalation study in rats (section 4.2.1).

4.4.4.1 Conclusions on classification and labelling

CLP Regulation:	**No classification**
Directive 67/548/EEC:	**No classification**

4.5 Corrosivity

Triadimenol was not corrosive when tested for skin and eye irritation

4.5.1 Conclusions on classification and labelling

CLP Regulation:	**No classification**
Directive 67/548/EEC:	**No classification**

4.6 Sensitisation

4.6.1 Skin sensitisation

The potential for triadimenol to induce skin sensitisation has been investigated in two guinea pig studies.

Table 15: Summary table of relevant skin sensitisation studies

Method	Doses	Results	Reference
Guinea pig/SPF, females, 20 in test group, 10 in negative control group Buehler test 80:20 mixture, purity 97.2% OECD 406 (1992), GLP	*Induction* 62.5% *Challenge* 62.5% Formulated in polyethylene glycol	0/20 animals were sensitized. The positive control substance, alpha hexyl cinnamic aldehyde, gave a positive response in 60% of the animals. Conclusion: non-sensitising	Vohr, 2005
Guinea pig/Pirbright white, 10/sex/group Maximisation test 80:20 mixture, purity 92.7% Similar to OECD 406 (1981), not GLP	*Induction* Intradermal: 2.5% Topical: 25% *Challenge* 25% Formulated in Cremophor EL	0/20 positive at 24 hours 1/20 animals gave a response (score 0.5) at 48 hours. Conclusion: non-sensitising There did not appear to be a positive control group.	Flucke, 1981

4.6.1.1 Non-human information

Triadimenol did not induce skin sensitisation reactions in any animals in a Buehler assay when it was tested at 62.5%. Appropriate responses were obtained in the positive and negative groups.

In a guinea pig maximisation test, triadimenol was negative for skin sensitisation. However, limitations of the study included the lack of: a positive control group; a justification for the concentrations used; and information on irritation (although the animals were pre-treated with 10% sodium lauryl sulphate).

4.6.1.2 Human information

No information available.

4.6.1.3 Summary and discussion of skin sensitisation

Triadimenol did not induce skin sensitisation in a well conducted Buehler study. Supportive evidence was obtained from a guinea pig maximisation test.

4.6.1.4 Comparison with criteria

The criteria for classification as a skin sensitiser (positive in ≥ 15% of animals in a Buehler/non-adjuvant assay, positive in ≥ 30% of animals in a guinea pig maximisation test/adjuvant assay) in the CLP Regulation as amended by the 2nd ATP and Directive 67/548/EEC were not met.

4.6.1.5 Conclusions on classification and labelling

CLP Regulation:	**No classification**
Directive 67/548/EEC:	**No classification**

4.6.2 Respiratory sensitisation

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

4.7 Repeated dose toxicity

The repeated-dose toxicity of triadimenol has been investigated in rats, mice, dogs and rabbits by the oral, inhalation and dermal routes.

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Rat

Table 16.1: Summary table of relevant repeated dose toxicity studies in the rat (oral)

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Oral (gavage) for 28 days Rats/Wistar, 20/sex/group 24 hours after the final dose, half the animals in each group were sacrificed. The remaining animals were observed for a further 28 days. 60:40 material, purity 98.5% Not guideline or GLP Thyssen & Kaliner, 1976	0, 5, 15, 45 mg/kg/d An extra group of 10/sex received 1.5 mg/kg/d, but there were limited investigations in this group	Terminal observations and samples for haematology and clinical chemistry were taken 24 hours, or, for the recovery animals, 28 days after the final treatment. There were no deaths, clinical signs or effects on body weight. Haematology, clinical chemistry and urinalysis values were similar between groups. Gross necropsy did not reveal any treatment-related findings, nor did a test to detect the presence of blood in faeces. Thyroid weights were slightly increased in high-dose males - absolute: 0%, 10%, 10%, 20%**; relative: 0%, 0%, 0%, 25%** in the 0, 5, 15, 45 mg/kg/d groups. In females, triadimenol had a statistically significant effect on ovary weights in all treatment groups, with increases of absolute: 0%, 14%**, 14%*, 20%**; relative: 0%, 18%**, 14%*, 18%** in the 0, 5, 15, 45 mg/kg/d groups. The increased weights of the thyroid in males and ovary in females were not associated with histopathological findings. Because of this, the small differences in absolute terms and the lack of a dose-response relationship in effects on ovary weights, the study authors considered that these organ weights were within the normal range. Histopathology of other organs and tissues did not reveal any treatment-related effects. Following the 4-week recovery period, there were no differences between exposed and control animals. The NOAEL was concluded to be 45 mg/kg/d.
Oral (gavage) for 28 days Rats/Wistar, 20/sex/group 80:20 (purity 98.3%) and 60:40 (purity 84.7%) materials tested Half the animals in each group were sacrificed at the end of the treatment period. The remaining animals were observed for a further 28 days. Not guideline or GLP Mihail & Vogel,	80:20 material: 0, 15, 45, 100 mg/kg/d 60:40 material: 0, 45, 100 mg/kg/d	There were no deaths. The only clinical sign noted was a slight increase in mobility that persisted for up to two hours after dosing and that occurred from day 3 onwards in those animals that received 45 or 100 mg/kg/d of either test substance. *Results obtained immediately after dosing period* Body weights, haematology and urinalysis parameters were unaffected by triadimenol. Slight reductions in various clinical chemistry parameters (AST, bilirubin in males; glucose in females) were stated by the study authors to be within the normal range of physiological variation, apart from those for creatinine, which were reduced in males by 19%** at 100 mg/kg/d and up to 19%* at 45 & 100 mg/kg/d 60:40 material. In females, creatinine was reduced by 10%*, 15%*, 27%** at 15, 45, 100 mg/kg/d; and by 19%** and 29%** at 45 & 100 mg/kg/d 60:40 material. Microsomal enzyme activities were higher (more marked in males) in liver samples after exposure to either test material ≥ 45 mg/kg/d. The following increases in activity were noted: P450 activity by up to 78%** in males and females; aminopyrine-N-DEM by up to 92%** in males and 58%** in females; O-DEM by up to 40%** in males and 34%** in females. There were marginal increases in liver weights at 100 mg/kg/d of both test materials. In males, the increases were 0% / 5% (absolute/relative), whilst in females they were up to 13%** / 11%**. Thyroid weights were not increased and differences in ovary weights were

1981		minimal: 0%, 6%, 5%, 13% (absolute) and 0%, 5%, 5%, 11% (relative) at 0, 15, 45, 100 mg/kg/d of 80:20 mixture; 8% & 16% (absolute) and 11% & 14% (relative) at 45 & 100 mg/kg/d 60:40 material. There were no other effects on organ weights. There were no treatment-related gross necropsy or histopathological findings. *Results obtained after 4-week recovery period* There were no clinical signs and no effects of treatment on body weight, haematology or urinalysis after the recovery period. There were slight reductions in urea (males and females), bilirubin (females only) and creatinine (up to 14% in males at 100 mg/kg/d; and up to 20% in females with 100 mg/kg/d 60:40 material). Microsomal enzyme induction in liver samples was similar between the groups, indicating that the enzyme induction was reversible. There were no notable gross necropsy findings (histopathology was not performed) and no differences in organ weights between the groups. The NOEL was 15 mg/kg/d.
Oral (dietary) for 90 days Rats/Wistar, 15/sex/group (30/sex control group) 60:40 material, purity 98% Not guideline or GLP Loeser & Kaliner, 1977	0, 150, 600, 2400 ppm Equivalent to Males: 0, 12, 49, 203 mg/kg/d Females: 0, 17, 71, 287 mg/kg/d	One female in the 600 ppm group died on day 83. The cause of death was myocardial necrosis and nephritis and was not thought to be treatment-related. There were no clinical signs of toxicity and food consumption was unaffected, although body weight gains were statistically significantly reduced in the high-dose groups of each sex. Haematology investigations were conducted at one month and three months. At the former, the only adverse finding was a slightly decreased haematocrit in high dose females. At the latter time, there were decreases in mean corpuscular haemoglobin (MCH) (by 7%**) and mean corpuscular volume (MCV) (by 13%**) in high-dose males, and decreased haematocrit (by 4%*) in high-dose females. The relative proportion of eosinophils was also reduced in high-dose females (by 86%*). No changes in clinical chemistry were noted at one and three months. There were no adverse findings at gross necropsy. Liver weights were increased by 1%, 1%, 7%* in males; and 0%, 3%, 17%** (absolute values) in females at 150, 600, 2400 ppm. Other organ weight effects were also recorded in high-dose females: absolute ovary weights were increased by 5%, -3%, 23%**; absolute kidney weights were increased by 8%, 2%, 10%* at 150, 600, 2400 ppm. There were no treatment-related histopathological findings in any organs or tissues. The NOAEL was 600 ppm, equivalent to 49-71 mg/kg/d.
Oral (dietary) for 90 days Rats/Sprague Dawley, 20/sex/group 80:20 material, purity 94% Not guideline or GLP Nishimura, 1983	0, 120, 600, 3000 ppm Equivalent to Males: 0, 8, 40, 209 mg/kg/d Females: 0, 9, 46, 221 mg/kg/d	There were no treatment-related deaths. In the high-dose groups, food consumption was reduced by up to 25%, and overall body weight gain was 11% lower in males and 24% lower in females. At 3000 ppm, decreased haemoglobin (by 4%**) and haematocrit values (by 4%**) in males and females were indicative of mild anaemia. Platelet counts were also lower in high-dose males (by 13%**). A lower percentage of reticulocytes (up to 25% reduction at 600 ppm) was also noted in males, although not in a dose-related pattern. Clinical chemistry changes associated with effects on the liver through lipid metabolism were identified at the high-dose level: there were increases in total cholesterol (by 39%**), phospholipid (by 18%*) and total protein (by 3%*) and decreases in albumin (by 7%**) and the albumin/globulin ratio (by 14%**) in females; decreased triglycerides (by up to 32%**) and free fatty acids (by up to 18%**) occurred in males and females. At gross necropsy, treatment-related effects on the liver were observed with a

dose-response relationship: enlarged liver in 1, 0, 2, 4 males and 0, 0, 1, 7 females (group sizes were 20); and accentuated lobular pattern in 0, 0, 2, 5 females at 0, 120, 600, 3000 ppm.

Absolute and relative liver weights were significantly increased by: absolute values of 0%, 0%, 10%*, 17%** in males and 0%, -1%, 9%*, 35%** in females; relative values of 0%, 2%, 7%**, 28%** in males and 0%, 3%, 13%**, 58%** in females at 0, 120, 600, 3000 ppm.

At histopathology of the liver, triadimenol was associated with an increased incidence and severity of fatty change and increased incidence of eosinophilic degeneration of hepatocytes, as recorded below.

	Males				**Females**			
mg/kg/d	**0**	**8**	**40**	**209**	**0**	**9**	**46**	**221**
Number of livers	18	19	18	19	20	20	20	20
Fatty change	1	3	5	15	2	4	9	18
Slight	1	3	4	4	2	4	9	5
Mild			1	9				5
Moderate				1				8
Severe				1				
Eosin. degen.	0	0	0	13	0	0	0	9
Slight				12				9
Mild				1				

The fatty changes were found mainly in the central to mid-zonal region in males and the mid-zonal to peripheral regions in females. Additionally, at 3000 ppm, one male had ground glass appearance and two had nuclear alteration (anisokaryosis).

There were no treatment-related adverse histopathological findings in other organs or tissues.

The NOAEL was 120 ppm (8-9 mg/kg/d).

*N.B. The values for NOAEL/NOEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting. * Statistically significant at $p \leq 0.05$. ** Statistically significant at $p \leq 0.01$*

In several rat studies, triadimenol targeted the liver, kidneys, ovaries and thyroid. There were no deaths below the guidance cut-off values for classification of ≤ 50 mg/kg/d that is specified in Directive 67/548/EEC and ≤ 100 mg/kg/d that is specified in CLP (90-day study in rats). No serious effects occurred below these values.

In a 28-day study, the only liver effects were microsomal enzyme induction (from 45 mg/kg/d) and increases in liver weight (at 100 mg/kg/d), neither of which persisted during a 4-week recovery period; these changes were indicative of adaptive rather than adverse changes. In one of the 90-day studies, liver weights were increased from 40 mg/kg/d. Clinical chemistry changes associated with effects on the liver through lipid metabolism only occurred at 209/221 mg/kg/d, as was the case for the gross necropsy findings (enlargement, accentuated lobular pattern). Upon histopathology, dose-related increases in the incidence and severity of fatty change (from 8/9 mg/kg/d) and eosinophilic degeneration of hepatocytes (at 209/221 mg/kg/d) were observed.

Apart from the liver, the only organs that were targeted in more than one study were the kidneys and the ovaries. Increased kidney weights were reported in one of the 90-day studies, but only above the guidance value (at 287 mg/kg/d). The effect on the ovaries was somewhat more consistent, in that increased organ weights were recorded after exposures for 28 days (both studies: from 5 mg/kg/d, but without a dose-response relationship with unspecified isomer composition; and from 15 mg/kg/d with the 80:20 mixture) and 90 days (at 287 mg/kg/d). This effect was reversible during a four-week recovery period that followed 28 days' administration. None of these changes in organ weight was associated with adverse gross or histopathology findings.

In one of the 90-day studies there was an indication of mild anaemia in the high-dose group (209/221 mg/kg/d).

Mouse

Table 16.2: Summary table of relevant repeated dose toxicity studies in the mouse (oral)

<table>
<tr><th>Method</th><th>Dose levels</th><th>Observations and remarks
(effects of major toxicological significance)</th></tr>
<tr><td>Oral (dietary) for 13 weeks

Mice/CD-1, 10/sex/group

Presumed to be 80:20 material, purity 97.4%

OECD 408, GLP

Schladt & Sander, 1998</td><td>0, 160, 500, 1500, 4500 ppm

Equivalent to

Males: 0, 25, 77, 235, 872 mg/kg/d

Females: 0, 31, 94, 297, 797 mg/kg/d</td><td>A limited histopathology was performed, since the study was initiated to find suitable dose ranges for a chronic study.

One male of the high-dose group died on day 4, but the cause of death was not established. There were no other deaths. Piloerection (5/10 males) and squatting position (7/10 males) occurred in the high-dose group, but otherwise there were no clinical signs of toxicity.

Food consumption was increased by 13% in high-dose males but at the end of the treatment period these animals had body weights that were 9%** (1500 ppm) and 13%** (4500 ppm) lower than controls; body weights were 9%** lower than controls in females of the 4500 ppm group.

The haematology investigations showed that the haematocrit was decreased by 7%* and the mean corpuscular haemoglobin increased by 8%** in high-dose females. In males, decreased leucocyte counts were recorded in the 1500 and 4500 ppm groups, with reductions of 21%* and 27%, respectively.

The clinical chemistry investigations on plasma revealed increases in enzymes that were indicative of effects on the liver. In both sexes, AST and ALT were increased from 500 ppm (AST up to 340%** increase, ALT up to 684%** increase at 4500 ppm). Glutamate dehydrogenase was increased in males from 160 ppm (but within the historical control range at this dose) and in females from 500 ppm (both over 1000%** increase at 4500 ppm). ALP was increased by 40%* in males at 4500 ppm. Decreases in total protein, albumin, cholesterol and bilirubin were evident in both sexes at various dose levels from 500 ppm.

Additionally, homogenized samples of liver were analysed for enzyme activity, with increases in the activities of aminopyrine-N-demethylase and cytochrome P-450 from 500 ppm. Increased triglyceride concentrations also showed a dose-response relationship from 500 ppm.

Gross necropsy of the high-dose male that died revealed black areas in the glandular stomach. There were no treatment-related gross necropsy findings in the other animals.

Triadimenol administration had effects on liver and adrenal weights. In males, absolute liver weights were increased by 37%** and relative weights by 59%** at 4500 ppm. In females, absolute liver weights were increased by 34%** and relative weights 51%** at 4500 ppm. Adrenal weights were reduced in the high-dose groups only in males (absolute weight reduced by 34%, relative by 22%) and females (absolute weight by 47%**, relative by 36%*).

The effects on organ weights of the liver and adrenals were associated with various histopathological findings in these organs. The incidences of the liver findings are presented below.
<table>
<tr><th></th><th colspan="5">Males</th><th colspan="5">Females</th></tr>
<tr><th>mg/kg/d</th><th>0</th><th>25</th><th>77</th><th>235</th><th>872</th><th>0</th><th>31</th><th>94</th><th>297</th><th>797</th></tr>
<tr><td>No. livers</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>Hypertrophy</td><td>0</td><td>0</td><td>3</td><td>9</td><td>9</td><td>0</td><td>0</td><td>0</td><td>3</td><td>9</td></tr>
<tr><td>Cytoplasmic vacuolation</td><td>0</td><td>0</td><td>0</td><td>3</td><td>9</td><td>0</td><td>2</td><td>1</td><td>4</td><td>8</td></tr>
</table>
</td></tr>
</table>

Single cell necrosis	0	0	0	1	8	0	0	0	3	9
Fat storage	0	1	2	8	9	1	4	3	8	10
Slight		1	2	4	2	1	4	3	6	7
Mild				4	6				2	3
Moderate					6					
Severe										

The liver hypertrophy mainly affected centrilobular areas, although the whole lobule was often involved in high-dose animals. The hypertrophic cells usually showed a dense and homogeneously oesinophilic cytoplasm with apparently reduced glycogen storage. The observed increases in cytoplasmic vacuolation were associated with increased incidences of fat storage. The severity as well as the incidence of single cell necrosis showed a dose-response relationship: at 1500 ppm, the effect was graded as minimal in 1/10 males and 3/10 females, whereas at 4500 ppm it was graded as minimal in 3/10 males and 5/10 females, and as slight in 5/10 males and 4/10 females. One of the high-dose males also had focal hepatocellular necrosis (graded as minimal).

Histopathology of the adrenals revealed that there were no vacuoles in the X-zone of the adrenal cortex in any of the high-dose females, with incidences of 5/8, 8/10, 7/9, 5/10, 0/9 at 0, 160, 500, 1500, 4500 ppm. The study authors considered the toxicological significance of this finding to be uncertain. There were no treatment-related findings in other organs or tissues, but investigations were limited to liver, spleen, adrenal glands, thyroid glands, femur, sternum, kidneys and testes/epididymides, plus organs/tissues with macroscopic findings.

The NOAEL was 160 ppm (25-31 mg/kg/d).

N.B. The values for NOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting.
** Statistically significant at $p \leq 0.05$. ** Statistically significant at $p \leq 0.01$*

The liver and adrenals were the target organs, as evidenced by changes in organ weights, liver enzymes and histopathology. Although effects on liver microsomal enzymes and glutamate dehydrogenase were recorded at 160 ppm (25/31 mg/kg/d), these were within the historical control ranges of the laboratory and so were not considered to be treatment-related. Additionally, there were no other indications of liver toxicity at this dose level. However, the effects at the next dose level (77/94 mg/kg/d) were regarded as treatment-related. Although liver enzyme activity was increased from this dose, adaptive changes of the liver, as evidenced by increased organ weight, were only apparent from 297 mg/kg/d. Findings at histopathology that were indicative of hepatotoxicity (necrosis) mainly occurred from 235/297 mg/kg/d, although increased fat storage was reported in all dose groups.

A further histopathological finding in female mice was the absence of vacuoles in the X-zone of the adrenal cortex at 797 mg/kg/d. The study authors noted that this finding had been recorded in a number of previous studies on substances with various chemical structures: it was not considered to be a rare occurrence. They explained that the X-zone of the adrenal cortex was a transient feature in young mice, and in females the regression of this zone was characterised by the development of large vacuoles.

Dog

Table 16.3: Summary table of relevant repeated dose toxicity studies in the dog (oral)

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Oral (dietary) for 13 weeks Dogs/Beagle, 4/sex/group 60:40 material, purity 98.5% Similar to OECD 409 (1981), not GLP Hoffmann & Kaliner, 1977	0, 150, 600, 2400 ppm Equivalent to 0, 3.75, 15, 60 mg/kg/d for males and females combined	Up to 24 hours elapsed between the final feeding and the terminal procedures (blood sample collection and necropsy). There were no deaths or clinical signs of toxicity. Food consumption was similar overall, but delayed food intake was observed in high-dose animals. There were no statistically significant changes in body weights. Haematology and urinalysis parameters were unaffected by treatment at weeks 7 and 13. Clinical chemistry investigations indicated possible liver effects. Alkaline phosphatase activity was slightly increased in all treated groups at week 13, but without a dose-response relationship. The level of ALT activity was slightly higher at 15 and 60 mg/kg/d in week 7 but not at termination. Plasma cholesterol levels were also slightly increased in these dose groups in both sexes in week 7 and in males in week 13. Activities of cytochrome P-450 and aminopyrine-N-demethylase in liver tissue were increased in high-dose males and females, but only those of N-demethylase had statistical significance (increased by 78%**). Gross necropsy was normal in all groups. The relative liver weight was increased in high-dose females (by 11%*), and the absolute and relative kidney weights were increased in high-dose males (absolute by 16%* and relative by 20%). There were no effects in other organs. Histopathology did not reveal any adverse findings; in particular, findings in the liver and kidney were normal. The NOAEL was 3.75 mg/kg/d.
Oral (dietary) for 6 months Dogs/beagle, 6/sex/group 80:20 material, purity 98% Not guideline or GLP Hoffmann, 1984	0, 10, 30, 100 ppm Equivalent to 0, 0.25, 0.75. 2.5 mg/kg/d	This study was a follow-up to a two-year chronic study in order to determine a clear NOAEL. As a result, histopathology was not performed. Up to 24 hours elapsed between the final feeding and the terminal procedures (blood sample collection and necropsy). Triadimenol exposure had no effects on any of the investigated parameters. In particular, body weights were unaffected. There were also no changes in alkaline phosphatase, aminopyrine-N-demethylase and cytochrome P-450 activities. Organ weights were unchanged and there were no notable gross necropsy findings. The NOAEL was 100 ppm (2.5 mg/kg/d).
Oral (dietary) for two years Dogs/beagle, 4/sex/group 60:40 material, purity 94.9% Not guideline or GLP Hoffmann & Vogel, 1984	0, 150, 600, 2400 ppm Equivalent to 0, 3.75, 15, 60 mg/kg/d	Up to 24 hours elapsed between the final feeding and the terminal procedures (blood sample collection and necropsy). There were no treatment-related deaths, clinical signs of toxicity or effects on reflexes, body temperature, pulse rate or ophthalmoscopy. One high-dose female was killed for humane reasons in week 22 and was found to have a 'deteriorating disease of the knee joints'. This was not considered to be treatment related. Food and water consumptions were not affected by triadimenol. Body weight gains were lower than controls in males and females in all treatment groups. It was reported that the body weight gains in the control animals were extremely high, being outside or only just within the mean plus two standard deviations of historical control data. The body weight gains of all treated groups were within the normal range. Haematology and urinalysis parameters were normal in all dose groups. Some effects on clinical chemistry were recorded. Alkaline phosphatase levels

		were consistently higher than controls in the high-dose groups from week 40 (up to 300% increase). At week 104, aminopyrine-N-demethylase activity was higher than controls in males and females from 15 mg/kg/d (up to 269%); and the activity of cytochrome P450 was increased in males at 60 mg/kg/d (by 71% compared with controls) and from 15 mg/kg/d in females (by up to 93%). There were no treatment-related effects on organ weights or gross necropsy and histopathology findings. The NOEL was 3.75 mg/kg/d.

N.B. The values for NOAEL/NOEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting.
** Statistically significant at $p \leq 0.05$. ** Statistically significant at $p \leq 0.01$*

In a 90-day dog study, slightly increased alkaline phosphatase activity and cholesterol levels were indicative of a moderate increase in liver activity. Consistent with this were increased liver weights, but these effects were not associated with adverse gross necropsy or histopathology changes, and so are considered to be adaptive rather than adverse. Kidney weights were increased in high-dose males only but, again, occurred in the absence of gross or histopathological changes.

In studies of longer duration but with lower doses, the only clear adverse effect was a change in some clinical chemistry parameters in a two-year study, which was suggestive of increased liver activity. This was not associated with changes in organ weights, gross necropsy or histopathology.

4.7.1.2 Repeated dose toxicity: inhalation

Table 16.4: Summary table of relevant repeated dose toxicity studies (inhalation)

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Inhalation for one week (five exposures) Rats/Wistar, 10/sex/group Nose-only exposure 14-day observation period 60:40 mixture, purity not stated Not guideline or GLP Thyssen & Kimmerle, 1976	0.064 and 0.32 mg/L for 4 hours per day	Test atmosphere concentration was determined by analysis. Particle size analysis was not performed. It was not indicated if the test atmosphere concentration was the maximum attainable. The methods and result were poorly reported. However, five 4-hour exposures did not result in any deaths, clinical signs or signs of irritation on the visible mucosa.
Inhalation for 3 weeks (5 days/week, total 15 exposures) Rats/Wistar, 10/sex/group Nose-only exposure Not guideline or GLP Isomer composition and purity not stated Kimmerle, 1976	0, 0.03, 0.068, 0.23 mg/L in aerosol form for 6 hours per day Test atmosphere analyses and particle size analyses were not fully reported	There were no deaths or clinical signs of toxicity in any group. Body weights, haematology and clinical chemistry determinations were unaffected by triadimenol. Urinalysis parameters were reported as being unchanged, but no data were presented. No treatment-related effects were noted on organ weights or gross necropsy and histopathology findings (samples for laboratory analysis were taken and animals were sacrificed 24 hours after the final test substance administration). The NOAEL was 0.23 mg/L.

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

Two repeated dose inhalation studies, in the rat, are available, in which triadimenol did not give rise to deaths or clinical signs. It also had no effects on the measured parameters, which included gross examination, histopathology and weight determination of the liver, kidneys, ovaries and adrenals.

4.7.1.3 Repeated dose toxicity: dermal

Table 16.5: Summary table of relevant repeated dose toxicity studies (dermal)

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Dermal for 3 weeks (5 days/week, total 15 exposures) Rabbits/New Zealand White, 6/sex/group 80:20 material, purity 98% Not guideline or GLP Heimann & Schilde, 1984	0, 50, 250 mg/kg/d in Cremophor EL/distilled water Applied to clipped skin and left uncovered for 6 hours (animals were immobilized), then washed off. The skin of 3 animals/sex was abraded 24 hours before 1st application so that oedema and slight erythema occurred.	There were no deaths or clinical signs of toxicity during the exposure period in any group. Body weights (measured weekly) were unaffected by treatment, as were haematology, clinical chemistry and urinalysis parameters at the end of the treatment period. Liver enzyme activity values at termination of the study were slightly higher than controls in the treatment groups, but a dose-response relationship was not evident and the values were within the laboratory's normal range for rabbits. There were no notable gross necropsy findings (animals sacrificed 24 to 48 hours after the final treatment). Likewise, relative and absolute organ weights and histopathology findings were unaffected. 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 dermal repeated-dose study is available in rabbits, in which two doses of triadimenol were tested. No clinical signs or skin irritation were noted, and there were no effects on the measured parameters, including those of the liver, kidneys, ovaries and adrenals.

4.7.1.4 Repeated dose toxicity: other routes

No information available.

4.7.1.5 Human information

No information available

4.7.1.6 Other relevant information

The chronic/carcinogenicity studies in rats and mice are presented in section 4.10. The non-tumour findings of note are summarised here.

In rats, increased liver weights were apparent at 106 mg/kg/d, which were not associated with any other adverse findings.

In mice, increased liver nodules were recorded in males at 60 mg/kg/d but not at the higher dose (340 mg/kg/d). Liver weights increased from 60 mg/kg/d and were associated with hypertrophy, with the severity of this effect being increased at 340 mg/kg/d. Fatty change in females was also reported at 472 mg/kg/d, and single cell necrosis from 60 mg/kg/d in males. In a second mouse study, increased liver weights, enlarged/swollen livers and nodular formations occurred at 300 mg/kg/d. Histopathology changes in the liver were only noted at this dose level.

4.7.1.7 Summary and discussion of repeated dose toxicity

After oral administration, the main target organ in rats, mice and dogs was the liver. At lower doses and with shorter durations of exposure, the liver effects were indicative of adaptive rather than toxic responses, consisting of increased organ weights (in some cases associated with hypertrophy) and liver enzyme activities. The effects were reversible after administration of triadimenol for 28 days. A progressive worsening of the liver effects (gross and histopathology findings that were evidence of toxicity) in 90-day and longer-duration studies were consistent with bioaccumulation. In 90-day studies, the only toxic effect that occurred below the guidance values was fatty change (from 8/9 mg/kg/d in rats) / increased fat storage (from 25/31 mg/kg/d in mice). In both cases, the changes at these doses were slight. After chronic administration for up to two years, there was no liver toxicity in dogs or rats, although single cell necrosis (slight to minimal, severity not increased compared with the controls) was reported in male mice in one study from 60 mg/kg/d and fatty change in female mice at 472 mg/kg/d.

In various oral studies, triadimenol also increased the weights of the kidneys, ovaries, thyroid and adrenals. Since there was no evidence of organ dysfunction, these organ weight changes do not justify classification, although they may indicate an endocrine-disrupting potential for triadimenol.

Inhalation and dermal administration of triadimenol did not result in any adverse effects.

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

Under Directive 67/548/EEC, classification as R48 is reserved for substances that cause serious damage to health, generally at or below the guidance value of 50 mg/kg/d (for a classification as harmful) obtained in an oral 90-day study in rats. In several repeated-dose oral studies of durations from 28 days to two years, the only serious effect recorded at doses below this guidance value was fatty change of the liver (in 90-day rat and mouse studies).

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

A classification of R48 is indicated when serious effects that meet the following descriptions occur at or below 50 mg/kg/d.

a) Substance-related deaths

There were no deaths below the guidance value.

b) Major functional changes in the central or peripheral nervous systems and/or other organ systems

There were no major functional changes in any organ systems.

c) Any consistent changes in clinical biochemistry, haematology or urinalysis parameters that indicate severe organ dysfunction

Although there were changes in some clinical chemistry parameters, these were indicative of increased liver activity as a result of an adaptive change, not of severe organ dysfunction.

d) Severe organ damage noted in microscopic examination following autopsy

This can include evidence that includes ‘severe morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction (e.g. severe fatty change in the

liver)'. Hepatic fatty change/increased fat storage was reported from 8/9 mg/kg/d, but at these dose levels it was graded as slight. Moderate and/or severe fatty change only occurred at doses well above the guidance value. No other effects indicative of severe organ damage (necrosis, fibrosis, granuloma formation in vital organs with regenerative capacity; evidence of appreciable cell death in vital organs incapable of regeneration) were reported.

Additionally, there were no generalised changes that involved several organ systems or severe changes in the general health status of the animals.

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

Directive 67/548/EEC:	**No classification**

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

Under CLP, STOT-RE is assigned on the basis of a substance demonstrating evidence of significant or severe toxicity, generally at or below the guidance value of 100 mg/kg/d (for a classification in category 2) obtained in a 90-day rat study. 'Significant' toxicity is taken to mean changes that clearly indicate functional disturbance or morphological changes that are toxicologically relevant. 'Severe' toxicity is considered to be more profound or serious and indicates changes that are of a considerably adverse nature with a significant impact on health.

In several repeated-dose oral studies of durations from 28 days to two years, the only effects that could be regarded as significant or severe and that were reported at doses below the guidance value were fatty change of the liver (in 90-day rat and mouse studies) and hepatocellular necrosis (in an 18-month mouse study). When the guidance value is adjusted from a 90-day study to one of 12-months' duration, a value of 25 mg/kg/d is obtained, which is clearly below the dose (60 mg/kg/d) at which hepatocellular necrosis occurred. Additionally, the necrosis was graded as slight to minimal in all groups, with no increase in severity from controls even at doses of up to 340/472 mg/kg/d. Therefore, this effect will not be considered further in deciding upon a classification for repeated-dose toxicity.

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

A classification of STOT-RE is indicated when toxic effects that may include the following descriptions occur at or below 100 mg/kg/d.

a) Morbidity or death resulting from repeated or long-term exposure

There were no treatment-related deaths or cases of moribund animals below the guidance value.

b) Significant functional changes in the central or peripheral nervous systems or other organ systems

There were no such changes in any organ systems.

c) Any consistent and significant adverse change in clinical biochemistry, haematology or urinalysis parameters

Although there were changes in some clinical chemistry parameters, particularly liver enzyme induction, at dose levels relevant for classification these were indicative of increased liver activity as a result of an adaptive change and were reversible. Such adaptive responses constitute a normal biochemical or physiological response and do not indicate classification.

d) Significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination

There were no such effects at doses below the guidance values.

e) Multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity

There were no such effects.

f) Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver)

Hepatic fatty change/increased fat storage was reported from 8/9 mg/kg/d, but at these dose levels it was graded as slight. Moderate and/or severe fatty change only occurred at doses well above the guidance value.

g) Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration

There were no such effects.

Additionally, there were no generalised changes that involved several organ systems or significant/severe changes in the general health status of the animals.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

CLP Regulation:	**No classification**

4.9 Germ cell mutagenicity (Mutagenicity)

The genotoxic potential of triadimenol has been investigated in several *in vitro* and *in vivo* studies.

Table 17: Summary table of relevant *in vitro* and *in vivo* mutagenicity studies

Method	Concentrations tested	Results	Reference
IN VITRO			
Bacterial reverse mutation (Ames) *S. typhimurium* TA98, 100, 1535, 1537 60:40 material, purity 93.7% Not guideline or GLP	With S9: 4 to 2500 µg/plate Without S9: 2500 µg/plate	**Negative** ± metabolic activation	Herbold, 1979a
Bacterial reverse mutation (Ames) and DNA repair test (rec$^-$ assay) Ames: *S. typhimurium* TA98, 100, 1535, 1537, 1538, *E. coli* WP2 *uvrA* rec$^-$ assay: *Bacillus subtilis* rec$^+$ strain H17 and rec$^-$ strain M45 Isomer composition not stated, purity 97.5% Not guideline, GLP	Ames test With and without S9: 7 test concentrations from 5 to 5000 µg/plate rec$^-$ assay Eight concentration from 50 to 10 000 µg/disk	Ames test. **Negative** ± metabolic activation rec$^-$ assay **Negative**	Tanahashi & Moriya, 1982
Bacterial reverse mutation (Ames) and DNA repair test (rec$^-$ assay) Ames: *S. typhimurium* TA98, 100, 1535, 1537, 1538, *E. coli* B/r try $^-$hcr rec$^-$ assay: *Bacillus subtilis* rec$^+$ strain NIG17 and rec$^-$ strain NIG45 80:20 material, purity 97.5% Not guideline, GLP	Ames test With and without S9: 5 to 5000 µg/plate rec$^-$ assay single concentration of 200 µg/disk	Ames test. **Negative** ± metabolic activation rec assay **Negative**	Nagane *et al.*, 1982
In vitro mammalian cell gene mutation test Mouse lymphoma cell line (L5178Y) 80:20 material, purity 97.5% Not guideline, GLP	With and without S9: 3.9 to 125 µg/ml in the 1st assay and 25 to 150 µg/ml in the 2nd assay	**Negative** ± metabolic activation	Cifone, 1982
In vitro unscheduled DNA synthesis assay Primary rat hepatocytes were isolated from male Fischer 344 rats. 80:20 material, purity 97.5% Not guideline, GLP	Ten concentrations ranging from 0.25 to 250 µg/ml	**Negative**	Myhr, 1982
E. coli Pol A_1^- test DNA deficient strain: *E. coli* p 3478 (pol A_1^-). DNA proficient strain: *E. coli* W3110 (pol A^+) 80:20 material, purity 97.5% Not guideline or GLP	Five concentrations in the range 62.5 to 1000 µg/plate	**Negative**	Herbold, 1981
In vitro sister chromatid exchange test Chinese hamster ovary cells Isomer composition not stated, but presumed to be 80:20. Purity 93%	Concentrations between 0.1 and 1000 µg/ml to test for cytotoxicity. With S9: 100 to 225 µg/ml	**Negative** ± metabolic activation	Putman, 1987

US EPA guideline, GLP	Without S9: 38 to 300 µg/ml		
IN VIVO			
In vivo micronucleus test (oral) Mice, NMRI, 5/sex/group 60:40 material, purity 93.7% Not guideline or GLP	Two doses of either 175 mg/kg or 350 mg/kg administered by oral gavage, 24 hours apart. Femoral bone marrow was prepared 6 hours after the second application.	**Negative**	Herbold, 1978b
In vivo micronucleus test (oral) Mice, NMRI, 5/sex/group 80:20 material, purity 96.5% Not guideline or GLP	Two doses of either 350 mg/kg or 500 mg/kg administered by oral gavage, 24 hours apart. Femoral bone marrow was prepared 6 hours after the second application.	**Negative**	Herbold, 1979b
Germ cell effects (rodent dominant lethal assay) Mice/NMRI, 50 males 60:40 material, purity 93.7% Not guideline or GLP	Single gavage dose of 500 mg/kg.	**Negative**	Herbold, 1978a

4.9.1 Summary and discussion of mutagenicity

Triadimenol was negative in a series of *in vitro* genotoxicity assays. Two *in vivo* micronucleus assays have been conducted in which triadimenol was also negative, although these assays included only one sampling time (of six hours, compared with the current OECD 474 guideline-recommended sampling times of 18-24 hours and 36-48 hours). However, the negative results in these two assays are supported by the result of a dominant lethal assay.

No information from humans or other relevant information is available

4.9.2 Comparison with criteria

There was no indication that triadimenol has a mutagenic effect on somatic or germ cells in several *in vitro* and *in vivo* assays. The criteria for classification for mutagenicity were not met.

4.9.3 Conclusions on classification and labelling

CLP Regulation:	**No classification**
Directive 67/548/EEC:	**No classification**

4.10 Carcinogenicity

The chronic toxicity and carcinogenic potential of triadimenol have been investigated in rats and mice.

Table 18: Summary table of relevant combined chronic/carcinogenicity studies

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Oral (dietary) 2 years Rats/Wistar, 60/sex 60:40 material, purity 94.9% Not guideline or GLP Krötlinger *et al*., 1982	0, 125, 500, 2000 ppm Equivalent to: males: 0, 5, 19, 77 mg/kg/d females: 0, 6, 25, 106 mg/kg/d	Treatment did not affect survival rates, which were ≥ 70% in all groups. There were no treatment-related clinical signs, and food consumption was similar between all groups. *Non-tumour findings* Body weights gains were lower (by up to 19%) and overall body weights were reduced (by up to 13%) throughout the study in high-dose males and females. Slightly reduced erythrocyte counts were recorded in high-dose females at 3 and 6 months but not at later time points, and slightly lower haemoglobin at 6 months but not at the other time points. Slightly reduced erythrocyte counts were recorded in high-dose males at 6 months only. All the values were reported to be within the normal physiological range. Various clinical chemistry findings were reported. AST and ALT were higher from 500 ppm; in the high-dose groups, they were consistently increased at most time points, with males affected to a greater extent (up to 135%** increase for AST, 142% for ALT). GLDH was increased only in high-dose males (by 300%**). Plasma urea was slightly increased from 500 ppm in both sexes (by up to 11%*), but without a consistent pattern. Creatinine levels were consistently lower in high-dose males (by up to 36%**). Glucose levels were higher in all treated groups at 104 weeks, with a dose-response relationship in females but not males. All the differences were stated to be within the normal physiological range. Cholesterol levels and urinalysis were unaffected by triadimenol. Gross necropsy of all animals did not identify any treatment-related effects. Liver weights were higher in high-dose females (absolute increase of 6%*, relative of 21%**). There were no other treatment-related effects on organ weights. The incidence of females with mucosal retention cysts in the stomach was increased in all treatment groups: 13%, 28%, 15%, 33% at 0, 125, 500, 2000 ppm, respectively. The severity was also increased: graded as minimal: 13%, 23%, 13%, 27%; graded as moderate: 0%, 5%, 1.7%, 7% at 0, 125, 500, 2000 ppm. There were no other non-neoplastic histopathological findings. *Tumour findings* The pattern of neoplastic findings did not indicate any relationship to treatment. The numbers of rats with tumours was similar between all the groups, the number of rats with benign or malignant tumours was not increased by treatment and the time to the first tumour was not shortened by treatment. The NOEL was 125 ppm (5-6 mg/kg/d).
Oral (dietary) 18 months Mice/CD-1, 50/sex/group 80:20 mixture, purity 96.8-97.6% OECD 451 (1981), GLP Schladt, 1998	0, 80, 400, 2000 ppm Equivalent to Males: 0, 11, 60, 340 mg/kg/d Females: 0, 17, 91, 472 mg/kg/d	Clinical chemistry investigations were not performed. The survival rate was unaffected by treatment and was 68-90% at 18 months. There were no clinical signs of toxicity. Food consumption was slightly increased in the high-dose males, by 5%, but was otherwise similar between the groups. *Non-tumour findings* Body weights of both sexes at the high dose were significantly lower than controls from week 2 and throughout the remainder of the study, with reductions of up to 21%** in males and 16%** in females. There were no consistent, toxicologically important findings from the haematology investigations. At gross necropsy, nodules were identified in the liver, but the incidence was only increased in the 60 mg/kg/d males: 6/50, 6/50, 14/50, 5/50 at 0, 11, 60, 340 mg/kg/d, respectively. The incidences of liver nodules in the females were: 1/50,

4/50, 3/50, 1/50 at 0, 17, 91, 472 mg/kg/d.

Liver weights were increased in males: absolute by 7%, 10%, 27% and relative by 7%, 13%**, 48%** at 11, 60 and 340 mg/kg/d. They were also increased in females: absolute by -2%, 5%, 15%** and relative by 1%, 6%, 27%** at 17, 91 and 472 mg/kg/d. There were no other treatment-related organ weight changes.

A number of treatment-related histopathological liver findings were recorded in males from 60 mg/kg/d and in females from 472 mg/kg/d. These are summarised in the table below. The increased incidence of diffuse/centrilobular hepatocellular hypertrophy was accompanied by a dose-related increase in the severity in the males only. A dose-related increase in severity was not noted for the other non-neoplastic histopathological findings. Hepatocellular vacuolation (observed in females only) was characterised by large intracytoplasmic vacuoles containing eosinophilic fluid. The accumulated pigment that was observed was yellow/brown in colour.

Liver tumours

There was an increased incidence of neoplastic findings in the liver of males of the 400 ppm group; however, there was no dose-related response. The neoplastic and non-neoplastic liver histopathology findings are summarised in the table below.

	Males				**Females**			
mg/kg/d	**0**	**11**	**60**	**340**	**0**	**17**	**91**	**472**
Number of livers	50	50	50	49	50	50	48	50
Hypertrophy (total)	5	8	34**	49**	2[t]	2	2	45**
Grade 1	0	1	0	0	0	0	0	0
Grade 2	1	7	31	7	1	1	1	23
Grade 3	4	0	3	33	1	1	1	22
Grade 4	0	0	0	9	0	0	0	0
Fatty change	8	12	7	5	5[t]	2	7	23**
Cellular vacuolation	0	0	0	0	0[t]	2	2	12
Inflammatory infiltration	31[t]	32	35	45**	36	41	32	43**
Pigment accumulation	7[t]	7	10	36**	29[t]	33	25	40**
Single cell necrosis	6[t]	9	20**	42**	8[t]	5	8	25**
Basophilic foci of cellular alteration	0[t]	3*	2	5**	0	1	0	2
Adenoma	7	5	10	5	1	1	2	0
Adenocarcinoma	0	3*	4*	2	0	0	0	0
Haemangioma	0	0	1	0	0	1	1	0
Haemangiosarcoma	0	1	1	1	0	2	0	0

Historical control data from the RITA database[1] are available for this strain of mouse. Four studies of two-year duration (performed at the same laboratory as the present study) gave a range of 2-19.4% for hepatocellular adenoma and 6-17.6% for hepatocellular carcinoma. Nine studies of 18-19 month duration performed in various laboratories (with start dates of -6 to +2 years from the present study) gave a range in males of 0-13.6% (mean 5.8%) for adenoma and 4-22% (mean 11.9%)

		for carcinoma. The combined historical control range for hepatocellular adenoma/carcinoma was 8-32%, whereas the combined incidence in the present study was 14%, 16%, 28%, 14% at 0, 11, 60, 340 mg/kg/d. *Ovarian tumours* The incidence of ovarian luteoma in females was: 0/49[t] (0%), 0/50 (0%), 0/48 (0%), 2/50 (4%). Historical control data are available in the RITA database[1] from studies conducted in CD-1 mice between -6 and +3 years of the date of the present study. There were no reports of ovarian luteoma in historical control data from seven studies of 18-month duration. For 13 studies of two-year duration, the historical control range was 0-10% (mean 1.7%). Of these studies, six of them were without any incidences of ovarian luteoma. In the remainder, the mean was 3.5%, with 1, 2 or 5 animals being affected in each study. Taking all the historical control data together, this tumour occurred in 13 out of 1112 females. There were no other tumour findings of note. The total number of tumours, the incidence of benign and malignant tumours and the time of their appearance were not changed by triadimenol. The NOAEL for all effects was 80 ppm (11 mg/kg/d in males). The NOAEL for carcinogenicity was 2000 ppm (340-472 mg/kg/d).
Oral (dietary) 2 years Mice/CF_1/W 74, 50/sex/group 60:40 material, purity 94.9% Not guideline or GLP Bomhard & Loeser, 1982	0, 125, 500, 2000 ppm Equivalent to 0, 19, 75, 300 mg/kg/d for males and females	This study had the following deficiencies: there was not a histopathological investigation of a full range of organs and tissues; thorough investigation of abnormalities identified at the 24-month differential blood count could not be completed because of fading of the slides and the possibility that artefacts had been introduced during preparation; up to 50% of thyroids were not available for histopathological examination. Survival was unaffected by treatment and was 68-80% at 18 months, and 22-38% at 24 months. There were no clinical signs of toxicity and food consumption was similar between all groups. *Non-tumour findings* There were treatment-related effects on body weights and body weight gains at different time points from 19 mg/kg/d; these parameters were lower than controls for high-dose males throughout the study (up to 15% reduction in body weight, 40% reduction in body weight gain) and for high-dose females for the majority of the study (up to 11% reduction in body weight, 37% reduction in body weight gain). Body weight gains of mid-dose females were reduced by 16% over the duration of the study. There were no obvious haematology findings at 12 and 24 months, although blood smears (on 10/sex/group) at 24 months revealed some unusual findings. Howell-Jolly bodies were observed in all females (including controls), along with polychromatophilia in a single 19 mg/kg/d female. Howell-Jolly bodies and polychromatophilia were recorded in 9/10 high-dose and one 75 mg/kg/d males. Howell-Jolly bodies and polychromatophilia with basophilic stippling were observed in separate, single males at 19 mg/kg/d. Further investigation was prevented because of technical problems. Changes in clinical chemistry parameters at 12 and 24 months were suggestive of adverse liver effects. AST was markedly increased in high-dose animals (by up to 364%**), as was ALT (by up to > 800%**). Cholesterol was reduced in high-dose groups of both sexes at 12 months but only in the males at 24 months (up to 31%** reduction at 300 mg/kg/d). Alkaline phosphatase was increased by up to 250%** in both high-dose groups. At 12 months, total protein was slightly lower in the high-dose groups, but there were no differences from the controls at 24 months. Urea was slightly increased in females of the dosed groups at 24 months, but without a clear dose-response relationship. The only findings of note at gross necropsy were an increased incidence of enlarged or swollen livers and/or nodular formations in the liver in high-dose animals. Liver weights were markedly increased in these animals: in males, the

absolute and relative weight increases were 50%** and 66%**, respectively, whilst those in females were 73%** and 71%**, all at 300 mg/kg/d.

Histopathological findings were observed in the liver and the thyroids. The non-neoplastic findings are recorded together with the neoplastic findings in the table below. In the liver, hyperplasia in high-dose males and hyperplastic nodules in high-dose females were increased, but the incidence of hypertrophy was not increased. In high-dose males, there was an increased incidence of cystic thyroids. This lesion was described as being characterised by the presence of cystic changes in the follicles or in some cases by coalescence of one or two follicles that had also undergone cystic changes. The thyroids were frequently not available for examination, either because they were missing or had undergone autolysis. There were no adverse ovarian findings.

Tumour findings

The incidence of hepatocellular adenomas was increased in females in a dose-response relationship (see table below). In females, hepatocellular adenomas were observed in animals that died or were killed between 613 and 735 days at 75 mg/kg/d, and between days 501 (1 animal) and 735 at 300 mg/kg/d. In males, hepatocellular adenomas were observed between 573 and 734 days in controls and between days 576 and 734 at 300 mg/kg/d. The historical control range for this tumour in CF1 mice was 0 to 25% in males and 0 to 12% in females (8 studies conducted in the same laboratory from 2 years before to 2 years after the triadimenol study). In a study conducted concurrently with the triadimenol study, hepatocellular adenomas occurred in 25% of the male controls and 12% of the female controls.

The incidence of hepatocellular adenocarcinomas was not increased by triadimenol.

There was no increase in the incidence of thyroid or ovarian tumours.

Incidences of neoplastic and non-neoplastic liver and thyroid findings

	Males				**Females**			
mg/kg/d	**0**	**19**	**75**	**300**	**0**	**19**	**75**	**300**
Number of livers	50	50	50	50	50	50	50	50
Hypertrophy	0	0	1	1	1	2	1	1
Hyperplasia (focal)	0	0	0	3	0	0	0	0
Hyperplastic nodules	8	6	9	10	2	1	1	7
Hepatocytic hyperpigmentation	4	0	0	9	5	0	0	5
Necrosis	2	0	0	1	0	0	1	0
Adenoma	5	4	5	8	0	0	4	6*
Adenocarcinoma	3	0	0	1	1	0	1	0
Cystadenoma	1	0	0	0	0	0	0	0
Angioadenoma	0	0	0	0	0	0	1	0
Number of thyroids	28	24	34	39	36	36	31	35
Cysts	2	2	2	10	3	3	1	3
Adenoma	0	1	0	0	0	0	0	0

Overall, there was no treatment-related increase in the total incidence of neoplastic

		findings. The NOAEL was 19 mg/kg/d.

*N.B. The values for NOAEL/NOEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting. * Statistically significant at $p \leq 0.05$. ** Statistically significant at $p \leq 0.01$. [t] Statistically significant ($p \leq 0.05$)in a trend test*

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

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

Rat

Reductions in body weights and body weight gains in treated rats indicated that sufficiently high dose levels had been administered to assess triadimenol's carcinogenic potential. The non-neoplastic findings were consistent with those observed in the short-term repeated dose toxicity studies (section 4.7), in that the liver was the target organ (increased weights with some slight changes in clinical chemistry parameters, but in the absence of any gross or histopathology findings). The incidence and severity of mucosal retention cysts in the stomach was increased in females.

In this study there were no indications that triadimenol was carcinogenic.

Mouse

(i). Non-tumour findings

Reductions in body weights in treated mice indicated that sufficiently high dose levels had been administered to assess triadimenol's carcinogenic potential. Changes in clinical chemistry parameters that were suggestive of adverse liver effects were associated with increased liver weights and gross/histopathological liver findings: nodules, hepatocellular hypertrophy, hyperplasia, single cell necrosis (graded as slight and/or minimal in all groups, including the controls) and vacuolation. An increased incidence of cystic thyroids was reported in the second study but not in the first. Ovary weights were unaffected by treatment.

(ii). Malignant and benign liver tumours

At gross necropsy, the incidence of nodules in the liver was increased in the mid-dose male group. This was associated with an increased incidence of neoplastic lesions (hepatocellular adenocarcinoma) in this group, whereas this tumour type did not occur in any females. In males, the incidences of hepatocellular adenoma were 14%, 10%, 20%, 10% at 0, 11, 60, 340 mg/kg/d, whilst the incidences of hepatocellular carcinoma were 0%, 6%, 8%, 4%. Thus, there was not a dose-response relationship. At 60 mg/kg/d, the incidence of adenoma was outside the historical control range for studies of 18-19 months' duration (maximum 13.6%), although the incidence of carcinoma was not (historical control maximum 22%). Since the triadimenol study was of 18 months' duration, the historical control data for 18-19 month studies are more relevant than those of two years' duration. The incidence for combined adenoma/adenocarcinoma was within the historical control data for combined tumours; the study authors argued that it is somewhat arbitrary to distinguish the two tumour types histopathologically and so it is reasonable to combine adenoma/carcinoma. Survival in the high-dose group (90%) was higher than that of the mid-dose group (80%), and the timing of unscheduled deaths was similar between the two groups. Therefore,

the lack of increased tumours in the high-dose males is not explained by a reduced opportunity to develop liver tumours compared with the mid-dose male group. The toxicologically significant histopathology findings that were recorded in mid-dose males were recorded in higher incidences in the high-dose males, indicating that triadimenol's toxic effect on the liver was dose-related. Considering all the evidence, the conclusion is that the increased incidence of liver tumours in the mid-dose group was not related to triadimenol exposure.

Supportive information was provided by a second mouse study. There was no increase in the incidence of hepatocellular carcinoma in any treatment group. The incidence of hepatocellular adenoma was increased in females in a dose-response relationship (0%, 0%, 8%, 12% at 0, 19, 75, 300 mg/kg/d), but the incidence in the high-dose group was the same as that in the control female mice of a concurrently-run study (same strain of mouse and the same laboratory). An interim sacrifice was not included in the study design, so it is not possible to determine if exposure to triadimenol shortened the time to the first appearance of these tumours, although tumours were observed after similar numbers of days in control (between 573 and 734 days) and high-dose males (between 576 and 734 days) that died during and at the end of the study. Likewise, the times at which the tumours were observed were similar between females of the 75 and 300 mg/kg/d groups. Therefore, these tumours are considered to be incidental to triadimenol administration. The histopathological changes in the thyroid were not associated with thyroid tumours.

(iii.) Benign ovarian tumours

Ovarian luteomas occurred in 2/50 (4%) females of the high-dose group (472 mg/kg/d) in one study. This incidence was higher than that from historical control data derived from several studies of 18-months' duration (0%) but within the historical control range derived from studies of 24-months' duration (0-10%). The study pathologist noted that this tumour type is rare, but that when it occurs, there may be multiple spontaneous occurrences within a study (only approximately one half of the control studies accounted for all the incidences of tumours). Additionally, the two lesions reported in the triadimenol study were re-examined, leading to the pathologist's conclusion that neither was completely in concordance with the IARC classification for ovarian luteoma (Mohr *et al*., 2001): one lesion was possibly a 'sex cord stromal tumour (mixed)'; the second was a borderline neoplastic lesion and was possibly a sex cord stromal hyperplasia.

4.10.1.2 Carcinogenicity: inhalation

No information available.

4.10.1.3 Carcinogenicity: dermal

No information available.

4.10.2 Human information

No information available.

4.10.3 Other relevant information

Triadimenol was negative in a series of *in vitro* and *in vivo* assays to detect its genotoxic potential (section 4.9).

4.10.4 Summary and discussion of carcinogenicity

The available information on the carcinogenic potential of triadimenol is provided by three oral studies in which there were increased incidences in liver and ovarian tumours in mice. From the rat study there was no indication that triadimenol had a carcinogenic potential.

In a mouse study, there were increased incidences of benign and malignant liver tumours only in the mid-dose male group. When the two tumour types were combined, the incidence was within the contemporary historical control data. This, together with the absence of a dose-response relationship, suggests that they were incidental to triadimenol exposure. Additional support for the tumours being spontaneous rather than treatment-related was provided by the survival and histopathology data, which indicated that high-dose males had at least an equal opportunity to develop tumours and exhibited greater hepatocellular toxicity than the mid-dose males. Benign liver tumours also occurred in a second mouse study, in a dose-response relationship in females only. The observed incidences were within the normal range for this mouse strain. There were no reports of benign or malignant liver tumours in the rat study.

A low incidence (2/50, 4%) of ovarian tumours was reported in one mouse study at doses of 472 mg/kg/d; tumours of this type were not found in the second mouse study or in rats. The tumours were not associated with effects on ovary weights or histopathology, but were outside the historical control range for studies of the same duration. Ovarian luteoma is recognised to be a rare tumour, although clustered occurrences in the historical control data suggest that when it does arise, there may be multiple spontaneous occurrences within a study. On re-evaluation of the two lesions, the pathologist was of the opinion that neither was a clear-cut luteoma.

4.10.5 Comparison with criteria

Two tumour types in one species (the mouse) occurred in two studies in the absence of severe toxicity but with reductions in body weights of 11 to 21% (reductions in body weight gain of up to 40%). In neither mouse study was the total number of tumours increased by exposure to triadimenol.

There is no evidence that triadimenol induces tumours in humans, so category 1A is not appropriate.

Triadimenol is non-genotoxic, which lowers the level of concern for classification. Although increased incidences of liver tumours were observed in one sex in each study (with no dose-response in the male mice), the increased incidences in both studies were within the historical control ranges for those strains of mice; therefore, a causal relationship between triadimenol administration and liver tumour induction was not established and a classification for carcinogenicity is not proposed based on the liver findings. Classification in Category 1B is based on ‘sufficient’ evidence of carcinogenicity: benign/malignant neoplasms in a) two or more species of animals; or b) two or more independent studies in one species conducted at different times or in different laboratories or under different protocols. Since neither of these criteria was met, classification in this category is not appropriate .

It therefore remains to decide if the ovarian tumours best meet the criteria for Category 2 or no classification. Classification in Category 2 is based on ‘limited’ evidence of carcinogenicity where the data suggest a carcinogenic effect but are limited for making a definitive evaluation. Two cases of benign ovarian luteoma occurred in female mice exposed to 472 mg/kg/d triadimenol. This was a dose at which body weight gain was reduced by > 10%, indicating that the maximum tolerated dose was exceeded. Given the uncertainties over the significance of the finding (reports of multiple

spontaneous occurrences within a study) and the pathologist's indeterminate diagnosis of the lesions as luteomas, the overall conclusion is that the data do not suggest a carcinogenic effect and thus classification is not warranted.

4.10.6 Conclusions on classification and labelling

CLP Regulation:	**No classification**
Directive 67/548/EEC:	**No classification**

4.11 Toxicity for reproduction

The reproductive toxicity of triadimenol has been investigated in two-/multi-generation and developmental toxicity studies.

4.11.1 Effects on fertility

Two multi-generation studies have been conducted in rats.

Table 19: Summary table of relevant multi-generation studies

<table>
<tr><th>Method</th><th>Dose levels</th><th>Observations and remarks
(effects of major toxicological significance)</th></tr>
<tr><td>Oral (dietary)
Multi-generation
Rats/Long Evans, 10 male, 20 female/group
60:40 material, purity assumed to be 94.9%
Not guideline or GLP
Loeser & Eiben, 1982</td><td>0, 125, 500, 2000 ppm
Equivalent to 0, 15, 60, 240 mg/kg/d in males and females
Administered during 70-day pre-mating, mating at age 100 days, gestation and lactation periods</td><td>
The study had a number of deficiencies: food consumption was not measured, so test compound intakes were estimates; fertility of individual males was not determined since females were mated with more than one male; reproductive tissues were not examined histologically; sperm parameters were not examined; mating performance of females was not determined by vaginal smear; pregnancy status was not confirmed (females that did not produce young were assumed to be pregnant if they had clearly gained weight during mating and lost over 30 g three weeks after mating); gross necropsy was not performed on all generations.
Parental toxicity
There were no treatment-related deaths or clinical signs of toxicity in any generation.
Triadimenol had adverse effects on parental body weights, with a worsening of the effects through the generations. Body weight gains of the high-dose F_0 parents were reduced up to the time of the first mating and continued to be reduced in high-dose females up to the second mating. The body weights of the high-dose F_{1B} animals were reduced at weaning and remained lower up until the time of the first mating; the body weights of the mid-dose F_{1B} females were also slightly reduced up to the first mating. The body weights between weaning and the first mating of the F_{2B} generation were similarly affected by exposure to triadimenol, with males of the mid- and high-dose groups being affected. In this generation, females in all the dose groups were affected. Maternal body weights at the time of the first mating are shown below, in the table under developmental toxicity.
Fertility effects
Triadimenol administration consistently reduced fertility in all three generations in a dose-related pattern (apart from the second mating of F_1 animals). The fertility data are presented in the table below.
<table>
<tr><th>mg/kg/d</th><th>0</th><th>15</th><th>60</th><th>240</th></tr>
<tr><td></td><td colspan="4">F_0: first mating (to produce F_{1A})</td></tr>
<tr><td>No. pregnant/no. per group</td><td>17/20</td><td>16/20</td><td>14/19</td><td>4/20</td></tr>
<tr><td>Pregnancy rate (%)</td><td>85</td><td>80</td><td>73.7</td><td>20**</td></tr>
<tr><td></td><td colspan="4">F_0: second mating (to produce F_{1B})</td></tr>
<tr><td>No. pregnant/no. per groups</td><td>16/18</td><td>16/20</td><td>14/19</td><td>13/19</td></tr>
<tr><td>Pregnancy rate (%)</td><td>88.9</td><td>80</td><td>73.7</td><td>68.4</td></tr>
<tr><td></td><td colspan="4">F_1: first mating (to produce F_{2A})</td></tr>
<tr><td>No. pregnant/no. per group</td><td>20/20</td><td>20/20</td><td>14/20</td><td>4/8</td></tr>
<tr><td>Pregnancy rate (%)</td><td>100</td><td>100</td><td>70*</td><td>50**</td></tr>
<tr><td></td><td colspan="4">F_1: second mating (to produce F_{2B})</td></tr>
<tr><td>No. pregnant/no. per group</td><td>16/19</td><td>17/20</td><td>6/20</td><td>4/7</td></tr>
<tr><td>Pregnancy rate (%)</td><td>84.2</td><td>85</td><td>30**</td><td>57.1</td></tr>
</table>
</td></tr>
</table>

			F_2: first mating (to produce F_{3A})		
		No. pregnant/no. per group	17/20	20/20	7/14	5/15
		Pregnancy rate (%)	85	100	50	33.3**
			F_2: second mating (to produce F_{3B})		
		No. pregnant/no. per group	18/20	15/20	10/14	7/14
		Pregnancy rate (%)	90	75	71.4	50*

Developmental toxicity

Developmental landmarks were not assessed, although examination of pups for grossly visible malformations after birth or during lactation did not reveal any malformed pups; however, this observation is of limited value, since dams may eat obviously malformed pups soon after birth.

Triadimenol administration was associated with reduced litter size at birth, reductions in the pup viability indices and reduction in pup weight, although these effects generally occurred together with reductions in maternal body weight. Changes in maternal body weight at the first mating, total litter size at birth, pup viability data and changes in pup weights at birth and after 28 days for all the litters are presented below.

mg/kg/d	**0**	**15**	**60**	**240**
	F_0: first mating (to produce F_{1A})			
Maternal body weight	0%	+1%	-5%	-19%**
Litter size at birth	11.9	11.6	10.6	4.2%*
Pup weight at birth	0%	0%	0%	0%
5d viability index (%)	90.1	85.4	79.9*	41.2**
28d viability index (%)	90.1	79.3*	93.3	14.3**
Pup weight at 28 days	0%	0%	0%	-28%**
	F_0: second mating (to produce F_{1B})			
Litter size at birth	11.5	10.7	10.6	3.8*
Pup weight at birth	0%	0%	0%	-13%
5d viability index (%)	90.8	82.0*	77.2*	81.6
28d viability index (%)	95.6	90.2	91.0	52.6**
Change in pup weight at 28 days	0%	0%	0%	-23%**
	F_1: first mating (to produce F_{2A})			
Maternal body weight	0%	+2%	-8%**	-15%**
Litter size at birth	12.1	11.2	10.1	10.0
Pup weight at birth	0%	0%	0%	0%
5d viability index (%)	87.2	85.3	76.6*	62.5**
28d viability index (%)	98.9	93.9*	70.3**	63.6**
Pup weight at 28 days	0%	0%	0%	-33%**
	F_1: second mating (to produce F_{2B})			

		<table><tr><td>Litter size at birth</td><td>12.7</td><td>10.5</td><td>6.2*</td><td>9.7</td></tr><tr><td>Pup weight at birth</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td></tr><tr><td>5d viability index (%)</td><td>88.7</td><td>81.6</td><td>64.9**</td><td>84.6</td></tr><tr><td>28d viability index (%)</td><td>97.3</td><td>91.3</td><td>95.8</td><td>73.3**</td></tr><tr><td>Pup weight at 28 days</td><td>0%</td><td>0%</td><td>0%</td><td>-21%*</td></tr><tr><td></td><td colspan="4">**F_2**: first mating (to produce F_{3A})</td></tr><tr><td>Maternal body weight</td><td>0%</td><td>-7%*</td><td>-9%**</td><td>-24%**</td></tr><tr><td>Litter size at birth</td><td>11.9</td><td>9.5</td><td>5.7*</td><td>6.8*</td></tr><tr><td>Pup weight at birth</td><td>0%</td><td>-11%</td><td>-20%**</td><td>-20%*</td></tr><tr><td>5d viability index (%)</td><td>89.7</td><td>66.5**</td><td>2.5**</td><td>11.8**</td></tr><tr><td>28d viability index (%)</td><td>70.7</td><td>53.0</td><td>0</td><td>0</td></tr><tr><td>Pup weight at 28 days</td><td>0%</td><td>0%</td><td>-</td><td>-</td></tr><tr><td></td><td colspan="4">**F_2**: second mating (to produce F_{3B})</td></tr><tr><td>Litter size at birth</td><td>10.3</td><td>8.5</td><td>11.0</td><td>3.9**</td></tr><tr><td>Pup weight at birth</td><td>0%</td><td>0%</td><td>0%</td><td>-16%*</td></tr><tr><td>5d viability index (%)</td><td>81.6</td><td>74.0</td><td>96.4**</td><td>29.6**</td></tr><tr><td>28d viability index (%)</td><td>93.9</td><td>93.7</td><td>88.8</td><td>100.0</td></tr><tr><td>Pup weight at 28 days</td><td>0%</td><td>-14%</td><td>-26%*</td><td>-29%</td></tr></table> Sex ratios in pups of F_1 parents were M/F 52/48, 48/52, 57/43, 76.5/23.5 at the first mating and 50/50, 58.7/41.3, 55.7/44.3, 51/49 at the second mating at 0, 15, 60, 240 mg/kg/d. The distortion of the sex ratio at 240 mg/kg/d in the first mating may have been a sampling error resulting from the small group size. The sex ratios of all the litters in the subsequent generations were unaffected by triadimenol, and so the finding at the first mating of F0 animals was unlikely to be treatment related. Gross necropsy was limited to animals that died prematurely and F_{2B} parents / F_{3B} offspring (1/sex/dam/group at 4 weeks old). No treatment-related gross necropsy findings were recorded. Liver, kidney, testicle or ovary weights were examined in the F_{2B} parents. Liver and kidney weights were unaffected relative to body weight, but, even accounting for the lower body weights of these animals compared with controls, testes weights were elevated at 60 and 240 mg/kg/d (relative values of 124% and 142% of the controls at 60 and 240 mg/kg/d), whilst ovary weights were elevated at 240 mg/kg/d (relative value of 123% compared with the controls). Histopathological investigations were not performed. A NOAEL was not identified.
Oral (dietary) Rats/Wistar/ 10 male, 20 female/group 80:20 mixture, purity 97.5% Reference made to OECD 416 (1983), not	0, 20, 100, 500 ppm Equivalent to F_0: males 0, 1.7, 9, 42; females 0, 2.2, 11, 57 mg/kg/d F_1: males 0, 1.2, 6, 29; females 0, 1.8,	Histopathology was not performed on animals that failed to induce pregnancy or failed to become pregnant. Assessment of male fertility was limited, because each female was mated with multiple males. Also, sperm parameters and developmental landmarks were not assessed. Vaginal smears to detect the presence of sperm were taken from F_{1B} females (but not from F_0 animals) to confirm that mating had occurred. *Parental toxicity* There were no treatment-related deaths or clinical signs of toxicity. The body weights of F_0 parent animals were not affected by triadimenol. However, the high-dose F_{1B} animals had lower body weights at weaning (by up

GLP

Loeser & Eiben, 1984

9, 39 mg/kg/d

Administered to F_0 through 100-day pre-mating period, mating, gestation and lactation.

to 6%) that remained lower to the start of mating, although body weight gains in the pre-mating period were comparable with controls. The body weights of these animals were significantly lower during the period between the first and second mating in both sexes, and remained lower for the remainder of the study (up to 9% reduction).

Fertility effects

Fertility of the F_0 parents was unaffected by dosing with triadimenol. There was a slight effect on the fertility of the F_1 parents of the high-dose group as a result of a lower rate of insemination, although the effects were inconsistent. The study report stated that three high-dose females that failed to become pregnant in either of the first two matings produced normal-sized litters in a third mating, although no further details were provided. The fertility data are presented in the table below.

mg/kg/d (female)	**0**	**2.2**	**11**	**57**
	F_0: first mating (to produce F_{1A})			
No. pregnant/no. per group	19/20	19/19	20/20	20/20
Fertility index	95	100	100	100
	F_0: second mating (to produce F_{1B})			
No. pregnant/no. per group	19/20	19/19	18/20	18/20
Fertility index	95	100	90	90
mg/kg/d (female)	**0**	**1.8**	**9**	**39**
	F_1: first mating (to produce F_{2A})			
No. pregnant/no. per group	17/19	16/20	14/20	14/20
Insemination index[1]	95	95	90	70
Fertility index[2]	90	80	70	70
	F_1: second mating (to produce F_{2B})			
No. pregnant/no. per group	15/18	15/20	16/20	15/20
Insemination index	100	95	85	80
Fertility index	83	75	80	75

Developmental toxicity

There was no effect on maintenance of pregnancy or duration of gestation. Total litter sizes at birth, changes in pup weights and viabilities at 5 and 28 days for the two generations are shown in the table below (there were no statistically significant differences).

mg/kg/d (females)	**0**	**2.2**	**11**	**57**

[1] Determined from vaginal smears to detect the presence of sperm = number of inseminated females / number of females in the group x 100

[2] = number of pregnant females / number of females in the group x 100

		F_0: first mating (to produce F_{1A})			
		Litter size at birth	9.3	10.5	11.2	9.9
		Pup weight at birth	0%	-2%	-5%	-5%
		5d viability index (%)	94.4	97.0	91.1	92.9
		28d viability index (%)	98.1	97.2	96.7	94.6
		Pup weight at 28 days	0%	-4%	-6%*	-5%
		F_0: second mating (to produce F_{1B})			
		Litter size at birth	9.8	10.3	9.9	9.3
		Pup weight at birth	0%	-2%	0%	-9%**
		5d viability index (%)	96.8	97.4	100	94.0
		28d viability index (%)	93.9	98.9	97.5	87.5
		Pup weight at 28 days	0%	-4%	-1%	-11%
		mg/kg/d (females)	**0**	**1.8**	**9**	**39**
		F_1: first mating (to produce F_{2A})			
		Litter size at birth	10.5	11.0	11.0	10.6
		Pup weight at birth	0%	+2%	+6%	+2%
		5d viability index (%)	78.7	93.7	96.8	96.0
		28d viability index (%)	79.8	89.3	92.7	88.5
		Pup weight at 28 days	0%	-12%*	+11%	-18%**
		F_1: second mating (to produce F_{2B})			
		Litter size at birth	11.5	10.1	10.8	10.3
		Pup weight at birth	0%	+4%	0%	+2%
		5d viability index (%)	90.7	97.4	92.5	89.0
		28d viability index (%)	87.7	96.9	81.6	90.4
		Pup weight at 28 days	0%	+1%	-7%	-3%

There was no effect of treatment on sex ratios.

Apart from animals that died prematurely, gross necropsy and histopathology were restricted to the F_{1B} parents and F_{2B} offspring. No treatment-related gross necropsy or histopathology findings were recorded.

The NOAEL for parental toxicity and reproductive effects was 100 ppm.

Gross necropsy of decedents, F_{1B} parents and F_{2B} offspring (1/sex/dam/group) did not show any treatment-related findings. In the high-dose F_{1B} parents, absolute and relative ovary weights were increased by 9% and 14%*, respectively, whilst in males of this group, relative testes weights were increased by 12%*. There were no corresponding histopathological findings in these organs.

The NOAEL for parental toxicity and reproductive effects was 11 mg/kg/d.

N.B. The values for NOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting.
** Statistically significant at $p \leq 0.05$. ** Statistically significant at $p \leq 0.01$*

4.11.1.1 Non-human information

A multi-generation study has been conducted in rats. Triadimenol was administered to F_0 males and females for a 70-day pre-mating period before being mated twice. The F_{1B} offspring were retained and subsequently mated twice, from which the F_{2B} offspring were mated twice to produce F_{3A} and F_{3B} pups. All matings within each generation were on the basis of one male to two females, with each female being kept together with three different males over a 20-21 day period. Standardisation of litter sizes to 10 pups took place on post natal day 5.

The pregnancy rate was consistently reduced at 60 and 240 mg/kg/d in both matings of the three generations, although it should be noted that in some generations the 240 mg/kg/d groups contained only small numbers of females for investigation, largely owing to the reduced pregnancy rate. As only limited investigations were performed (mating performance/pregnancy status of females was not confirmed; multiple males were housed with each female; no sperm investigations or histopathology of reproductive tissues), it was not possible to elucidate if the reduced number of pregnancies was the result of impaired mating or interference with another reproductive parameter.

In a two-generation study in rats, each generation was mated twice, with the first litter being sacrificed at weaning and the second generation being retained for mating. All matings were on the basis of one male to two females, with the male being replaced weekly over a three week period. Standardisation of litter sizes at a maximum of 10 pups took place on day 5. A dose-related reduction in the fertility index was recorded in the F_1 generation matings. The effects were less pronounced than those seen in the multi-generation study, but were consistent with the lower doses administered. At the high dose, the reduction in the fertility index was associated with a reduction in the insemination index, indicating that the effect on fertility may have been at least partially mediated through an interference with mating. The appearance and behaviour of all the treated rats did not differ from those of the controls, indicating that the reduced insemination indices were not a result of incapacitation.

4.11.1.2 Human information

No information available.

4.11.2 Developmental toxicity

The developmental toxicity of triadimenol has been investigated in several studies in rats and rabbits.

Table 20 : Summary table of relevant developmental toxicity studies

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Oral (gavage) Rats/Long Evans, 20-22 females/group 60:40 material, purity 93.7% Similar to OECD 414, not GLP Machemer, 1977	0, 10, 30, 100 mg/kg/d in 0.5% Cremophor EL on gestation days 6 to 15 (dams sacrificed on gestation day 20).	*Maternal toxicity* There were no deaths or clinical signs of toxicity in any group. There were 20 pregnant animals in each group (only data from pregnant animals were included). Body weights were reported as mean values for weight gain over the treatment and gestation periods rather than as actual body weights at different time points. Body weight gains during the treatment period were 100%, 101%, 95%, 76%** at 0, 10, 30, 100 mg/kg/d. Weight gains over the whole gestation period were slightly lower at 100 mg/kg/d only (96% of controls). Gross necropsy of dams was not performed. *Developmental toxicity* Litter data was presented only as mean values for each litter. There were no total litter losses or effects of treatment on the number of viable fetuses at day 20, sex ratio, number of resorptions or total number of foetuses. Mean foetal and placental weights of the high-dose group were higher than those of controls, and in this group there were fewer 'stunted' (weight <3 g) foetuses. There were no external or internal malformations at 100 mg/kg/d. A number of foetuses at lower dose levels exhibited malformations of the head (hypoplasia of telencephalon, anophthalmia or microphthalmia), but these were also noted in a control foetus (foetal incidence 1/215, 5/200, 13/215, 0/218 at 0, 10, 30, 100 mg/kg/d). They also tended to be grouped in a small number of litters (litter incidence 1/20, 1/20, 3/20, 0/20 at 0, 10, 30, 100 mg/kg/d). Individual skeletal alterations were not reported (numerical incidence data only). The number of fetuses that showed retarded skeletal development was not increased by triadimenol. The NOAEL for developmental effects was 100 mg/kg/d. The NOAEL for maternal toxicity was 30 mg/kg/d.
Oral (gavage) Rats/Wistar, 25 females/group 80:20 material, purity 97% OECD 414, GLP Becker *et al*., 1987a	0, 30, 60, 120 mg/kg/d in 0.5% Cremophor EL on gestation days 6 to 15 Dams were sacrificed on day 21	Statistical analysis of the findings was limited. *Maternal toxicity* There were no deaths, clinical signs of toxicity or abnormal gross necropsy findings in adult animals. Maternal body weight gains were reduced in the 60 and 120 mg/kg/d groups in the early part of the treatment period (up to day 11), in a dose-response relationship (see table below). Body weight gains over the remainder of the study were comparable to controls. Food consumption was similarly lower in the 60 and 120 mg/kg/d groups up to day 11, but thereafter equalled or exceeded the intakes of the controls. *Developmental toxicity* An increase in the rate of post-implantation loss (embryonic and foetal resorptions were increased) resulted in a reduction in the number of live foetuses at 120 mg/kg/d. Sex ratio and foetal weight were unaffected. Placental weight was not investigated. External abnormalities were recorded in a single foetus at 30 mg/kg/d and visceral abnormalities in a single foetus in each of the control and 30 mg/kg/d groups. Skeletal anomalies occurred with a higher combined incidence in dosed groups, although without a dose-response relationship (3.4%, 6.6%, 11.5%, 6.7% of foetuses were affected at 0, 30, 60, 120 mg/kg/d). There was also no dose-

<table>
<tr>
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<td>response relationship in the individual skeletal anomalies. These frequencies of anomalies were described by the study authors as being within the normal range for this strain of rats (historical control data for overall incidence of skeletal anomalies were not provided, but data for individual findings were available).

Individual numerical data for skeletal ossification were not reported (only mean values were provided), but triadimenol did not appear to have affected the extent of delayed or absent ossification.

There was a dose-related increase in the incidence of supernumerary ribs (in most cases bilateral); these were small in size, being less than half the size of full ribs.

The main findings relevant to developmental toxicity are recorded below.
<table>
<tr><th>mg/kg/d</th><th>0</th><th>30</th><th>60</th><th>120</th></tr>
<tr><td>Maternal body weight gain (day 6-11)</td><td>100%</td><td>100%</td><td>84%</td><td>58%</td></tr>
<tr><td>Live foetuses: per group</td><td>289</td><td>304</td><td>266</td><td>255</td></tr>
<tr><td>per dam</td><td>12.0</td><td>12.2</td><td>11.6</td><td>11.1</td></tr>
<tr><td>Embryonic resorptions:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>per group</td><td>18</td><td>17</td><td>19</td><td>32</td></tr>
<tr><td>% of implantations</td><td>5.9</td><td>5.3</td><td>6.6</td><td>11.1</td></tr>
<tr><td>per dam: mean</td><td>0.8</td><td>0.7</td><td>0.8</td><td>1.4</td></tr>
<tr><td>Foetal resorptions:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>per group</td><td>0</td><td>1</td><td>2</td><td>2</td></tr>
<tr><td>% of implantations</td><td>0</td><td>0.3</td><td>0.7</td><td>0.7</td></tr>
<tr><td>per dam: mean</td><td>0</td><td>0</td><td>0.1</td><td>0.1</td></tr>
<tr><td>total post-implantation loss:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>per group</td><td>18</td><td>18</td><td>21</td><td>34</td></tr>
<tr><td>% of implantations</td><td>5.9</td><td>5.6</td><td>7.3</td><td>11.8</td></tr>
<tr><td>per dam: mean</td><td>0.8</td><td>0.7</td><td>0.9</td><td>1.5</td></tr>
<tr><td>Supernumerary ribs: no. skeletons</td><td>146</td><td>152</td><td>139</td><td>135</td></tr>
<tr><td>14th rib (left): incidence</td><td>11.6%</td><td>16.4%</td><td>38.8%</td><td>51.1%</td></tr>
<tr><td>14th rib (right): incidence</td><td>13.0%</td><td>19.1%</td><td>41.0%</td><td>51.1%</td></tr>
</table>

The NOAEL for developmental toxicity was 30 mg/kg/d. The NOAEL for maternal toxicity was 30 mg/kg/d.</td>
</tr>
<tr>
<td>Oral (gavage)

Rats/Long Evans, 25 females/group

80:290 material, purity 95.2%

Not guideline or GLP</td>
<td>0, 10, 30 mg/kg/d in 0.5% Cremophor EL

on days 6 to 15 of gestation

Dams were sacrificed on day 20</td>
<td>Maternal toxicity

There were no treatment-related deaths or clinical signs in dams. Body weight gains of the high-dose group were slightly lower than those of controls over the treatment period (reduced by 14%) and over the whole gestation period (by 9%).

Gross necropsy was not performed on dams.

Developmental toxicity

The number of females with live litters and the number of foetuses per litter was unaffected by treatment. There was also no effect on post-implantation losses. A</td>
</tr>
</table>

<table>
<tr><td>Renhof, 1984</td><td></td><td>single foetus of < 3g was identified, in the high-dose group. Mean foetal weight was similar between groups but mean placental weight was increased (106% and 111%* of controls at 10 and 30 mg/kg/d, respectively).

Skeletal findings were reported as numerical incidences only, and individual data were not reported. The number of foetuses with minor skeletal deviations and malformations was not increased by triadimenol.

The NOAEL for developmental effects was 30 mg/kg/d. The NOAEL for maternal toxicity was 10 mg/kg/d.</td></tr>
<tr><td>Oral (gavage)

Rats/Crl;CD, 5 females/group

Assumed to be 80:20 mixture, purity was 95%

OECD 414 (1981), GLP

Clemens et al., 1990</td><td>0, 25, 60, 95, 130, 165 mg/kg/d in 0.5% carboxy-methyl-cellulose / 0.4% Tween 80 NF

on days 6 to 15 of gestation.

Dams were sacrificed on day 20.</td><td>Range-finding study.

Maternal toxicity

Reduced body weight gains were recorded during the treatment period at all dose groups: day 0-20 body weight gains were 100%, 96%, 82%, 76%, 73%, 81% at 0, 25, 60, 95, 130, 165 mg/kg/d.

Developmental toxicity

Post-implantation loss was increased from 130 mg/kg/d: 11%, 4%, 5.5%, 4.7%, 28.4%, 30.8% at 0, 25, 60, 95, 130, 165 mg/kg/d.

There was no clear effect on foetal weights.

1/4 litters of the 165 mg/kg/d group contained 1/15 normal foetuses and 14/15 malformed foetuses (14 with protruding tongue, 5 additionally with cleft palate). A skeletal examination was not performed.</td></tr>
<tr><td>Oral (gavage)

Rats/Crl;CD, 28 females/group

Assumed to be 80:20 mixture, purity was 95%

OECD 414, GLP

Clemens et al., 1990</td><td>0, 5, 15, 25, 60 mg/kg/d in 0.5% carboxy-methyl-cellulose / 0.4% Tween 80 NF

on days 6 to 15 of gestation.

Dams were sacrificed on day 20.</td><td>Maternal toxicity

There were no deaths or clinical signs of toxicity.

Lower food consumption from 15 mg/kg/d during the treatment period was associated with reduced body weight gains: final corrected body weight gains were 100%, 97%, 84%**, 91%, 78%** at 0, 5, 15, 25, 60 mg/kg/d. This effect was evident from the start of treatment, but body weight gains after the end of treatment were comparable between groups.

There were no treatment-related gross necropsy findings in dams, and serum enzyme activities (AST, ALT, alkaline phosphatase) were similar between groups. Absolute and relative liver weights were unaffected by triadimenol.

Developmental toxicity

The number of dams with live litters was similar (≥ 22) between groups. There were no instances of total litter loss or abortion, and the number of corpora lutea and implantations was similar between the groups. There was no evidence of post-implantation loss. The total number of foetuses, mean litter size, mean foetal weight and sex ratio were likewise unaffected by treatment. Median placental weight was increased at 60 mg/kg/d (0.63g compared with 0.52g in the controls); this was outside the historical control range of 0.50 – 0.55 g.

The incidence and pattern of external, visceral and skeletal malformations was not changed by treatment. Likewise, skeletal ossification was unaffected.

There was a dose-related increase in the incidence of extra ribs (no information is provided on the size of the extra ribs). The data are summarised in the table below.
<table>
<tr><th>mg/kg/d</th><th>0</th><th>5</th><th>15</th><th>25</th><th>60</th></tr>
<tr><td>Number of foetuses</td><td>191</td><td>157</td><td>174</td><td>168</td><td>198</td></tr>
<tr><td>Number of litters</td><td>28</td><td>22</td><td>25</td><td>25</td><td>28</td></tr>
<tr><td>Extra lumbar ribs
foetuses (litters)</td><td>1 (1)</td><td>6 (6)</td><td>6 (6)</td><td>13 (9)</td><td>42 (20)</td></tr>
</table>
</td></tr>
</table>

		foetal % (litter %): 0.5 (3.6) / 3.8 (27.3) / 3.4 (24) / 7.7** (36) / 21.2** (74.4) Cervical ribs foetuses (litters): 4 (4) / 2 (2) / 3 (3) / 6 (3) / 13 (9) foetal % (litter %): 2.1 (14.3) / 1.3 (9.1) / 1.7 (12) / 3.6 (12) / 6.6 (32.1) Extra ribs (combined) foetuses (litters): 5 (5) / 8 (8) / 9 (8) / 19** (10) / 55 (24)** foetal % (litter %): 2.6 (17.9) / 5.1 (36.4) / 5.2 (32.0) / 11.3** (40) / 27.8 (85.7)** Historical control data were provided from studies conducted in the same laboratory with the same strain of rat over the 8 years previous to the triadimenol study: foetal incidence = 0.5 – 15.7 %; litter incidence = 3.6 – 66.7%. When only the data from studies (n = 8) conducted up to 3 years before the current study were considered, the foetal incidence was 0.5 – 6.6% and the litter incidence was 3.6 – 38.5%. No data from studies performed concurrently with or after the present study were available. The NOAEL for developmental toxicity was 15 mg/kg/d. The NOAEL for maternal toxicity was 5 mg/kg/d.
Oral (gavage) Rabbits/Chin-chilla, 16 females/group Assumed to be 80:20 mixture, purity was 97% OECD 414 (1981), GLP Becker *et al*., 1987b	0, 8, 40, 200 mg/kg/d in 0.5% Cremophor EL on days 6 to 18 of gestation Dams were sacrificed on day 28.	*Maternal toxicity* There were no treatment-related deaths or gross necropsy findings amongst dams. Clinical signs were recorded at 200 mg/kg/d and included: excited appearance; hair loss; skin injuries attributed to excessive scratching and gnawing; abrupt motions of the head and licking of the forepaws and abdomen. In the 200 mg/kg/d group, food consumption was markedly reduced during the treatment period, followed by increased food consumption during the post-treatment period. These animals lost weight during days 6 to 9 and showed very low body weight gain over the treatment period (17g gain, compared with 309g gain in the controls). Body weight gain over the treatment period was also reduced at 40 mg/kg/d (272g gain). *Developmental toxicity* The number of dams with live litters was at least 14 in each group. Post-implantation loss, largely as a result of embryonic resorptions, was increased at 200 mg/kg/d (foetal resorptions were mostly unaffected). The historical control data for post-implantation loss from 21 studies conducted between 1985 and 1987 were: per group = 1 - 14; % of implantations = 0.7 – 10.4; mean per dam = 0.1 – 0.9. The values for embryonic resorptions from the same studies were: per group = 0 - 9; % of implantations = 0 – 6.7; mean per dam = 0 – 0.6. As a result of the resorptions, the number of live foetuses was lower in this group, as was foetal weight. Placental weight was not determined. Sex ratios were unaffected. The pattern and incidence of skeletal malformations was similar between the groups. The incidence of skeletal anomalies, mostly in the form of abnormal or incomplete ossification, was increased at 200 mg/kg/d. The treatment-related developmental findings are presented in the table below. **mg/kg/d: 0 / 8 / 40 / 200**

		<table><tr><td>Live foetuses: per group</td><td>128</td><td>103</td><td>112</td><td>95</td></tr><tr><td>per dam</td><td>8.0</td><td>6.9</td><td>7.5</td><td>6.3</td></tr><tr><td>Embryonic resorptions</td><td></td><td></td><td></td><td></td></tr><tr><td>per group</td><td>1</td><td>7</td><td>3</td><td>11</td></tr><tr><td>% of implantations</td><td>0.8</td><td>6.4*</td><td>2.5</td><td>10.1**</td></tr><tr><td>mean per dam</td><td>0.1</td><td>0.5</td><td>0.2</td><td>0.7</td></tr><tr><td>no. dams affected</td><td>1</td><td>3</td><td>3</td><td>6</td></tr><tr><td>Total post-implantation loss</td><td></td><td></td><td></td><td></td></tr><tr><td>per group</td><td>5</td><td>9</td><td>8</td><td>14</td></tr><tr><td>% of implantations</td><td>3.8</td><td>8.0</td><td>6.7</td><td>12.8*</td></tr><tr><td>mean per dam</td><td>0.3</td><td>0.6</td><td>0.5</td><td>0.9</td></tr><tr><td>no. dams affected</td><td>5</td><td>5</td><td>5</td><td>7</td></tr><tr><td>Weights of live foetuses (g)</td><td>35.2</td><td>35.6</td><td>34.8</td><td>33.3*</td></tr><tr><td>Skeletal anomalies</td><td></td><td></td><td></td><td></td></tr><tr><td>foetal incidence</td><td>0%</td><td>2.9%</td><td>1.8%</td><td>7.4%**</td></tr><tr><td>litter incidence</td><td>0%</td><td>20%</td><td>13.3%</td><td>42.9%**</td></tr></table> The NOAEL for developmental effects was 40 mg/kg/d. The NOAEL for maternal toxicity was 8 mg/kg/d.
Oral (gavage) Rabbits/New Zealand White, 20 females/group Assumed to be 80:20 mixture, purity 96% OECD 414 (1981), GLP Clemens *et al.*, 1992	0, 5, 25, 125 mg/kg/d in 0.5% carboxymethyl cellulose / 0.4% Tween 80 on days 6 to 18 of gestation. Dams were sacrificed on day 29.	*Maternal toxicity* There were no deaths or clinical signs of toxicity. Dams of the 125 mg/kg/d group lost weight over the treatment period (associated with reduced food consumption) and overall weight gains (days 0-29) of this group were significantly reduced compared with the controls (29%* lower). Food consumption and weight gains of the other dose groups were unaffected. There were no abnormal findings at gross necropsy of dams, and absolute and relative liver weights were similar between groups. *Developmental toxicity* The number of dams with live litters was similar between groups (at least 16). Litter size at 25 and 125 mg/kg/d was lower than controls, but this was attributed to lower numbers of corpora lutea combined with higher pre-implantation losses. The study authors noted that the numbers of corpora lutea and implantations in the controls were at the upper end of the historical control range (from 6 studies conducted within the previous 12 months) whilst the numbers from the 25 and 125 mg/kg/d groups were at the lower end. Post-implantation loss was not increased by treatment and there were no changes in the sex ratios. Mean foetal weights were increased at 25 and 125 mg/kg/d. Mean placental weight was increased only at 25 mg/kg/d. There were no adverse effects on external, visceral and skeletal abnormalities. An increased extent of skeletal ossification at 25 mg/kg/d reflected the significantly increased foetal weights in the group. The NOAEL for developmental effects was 125 mg/kg/d. The NOAEL for maternal toxicity was 25 mg/kg/d.

N.B. The values for NOAEL are provided for information only; they have been agreed by a PRAPeR Expert Meeting.
** Statistically significant at $p \leq 0.05$. ** Statistically significant at $p \leq 0.01$*

4.11.2.1 Non-human information

Information on litter size at birth, pup body weights, viability and growth after triadimenol administration to dams was obtained from a multi-generation and a two-generation study in rats (section 4.11.1). The multi-generation study (Loeser & Eiben, 1982) showed a pattern of increasing severity of effects on viability and growth through the generations, with both the 5-day (number of pups before litter reduction at day 5 / number live born x 100) and the 28-day (number surviving to day 28 / number after litter reduction on day 5 x 100) viability indices being severely reduced in all dose groups (15, 60 and 240 mg/kg/d) at the first mating of the F_2 animals. At this mating there was also a treatment-related reduction in the litter size and pup weight at birth in all the treatment groups. However, these results were not repeated at the second F_2 mating, and effects in all the generations at 15 mg/kg/d, and possibly also at 60 mg/kg/d, were likely to have been chance findings. In the high-dose group, all the findings were likely to be a consequence of the fairly severe maternal toxicity (as observed in the maternal body weights being decreased by up to 24%), which also increased through the generations.

In a two-generation study (Loeser & Eiben, 1984), there were some reductions in litter size at birth and pup viability that were more apparent at the second mating, but they were small, inconsistent and there was usually no dose-response relationship. A direct comparison of substance intake between the multi-generation and the two-generation study was not possible, since intakes in the first study were estimates based on guidance rather than measured values. However, from the estimated values, the intakes of triadimenol were less in the second study (the high-dose group in the two-generation study was less than the mid-dose group of the multi-generation study).

The number of post-implantation losses was increased in rats from 120 mg/kg/d and in rabbits at 200 mg/kg/d. The increased embryonic and foetal resorptions in rats (Becker *et al*., 1987a; Clemens *et al*., 1990) occurred in a dose-response relationship and were associated with maternal toxicity (reduced body weight gains). In rabbits (Becker *et al*., 1987b), the greater extent of embryonic resorptions compared with foetal resorptions in the high-dose group was consistent with the maternal toxicity (clinical signs and weight loss) noted in these animals, which was more marked during the early part of gestation.

In one rat developmental study (Machemer, 1977), a number of foetuses in the lower dose groups (10 and 30 mg/kg/d) exhibited malformations of the head, which tended to be clustered in a small number of litters, but there were no occurrences in the high-dose (100 mg/kg/d) group, even in the presence of maternal toxicity.

In several other developmental studies, there were dose-related increases in the incidences of supernumerary ribs (two studies, occurred from 5 mg/kg/d) and malformed foetuses (one study, at 165 mg/kg/d) in rats. In one study, the extra ribs were small (Becker *et al*., 1987a). In a second study (Clemens *et al*., 1990), the combined incidence of extra ribs exceeded the most relevant historical control data, with the increased incidence of extra lumbar ribs being particularly marked. There was no information on the size of the extra ribs, so there is uncertainty over the severity of the effect. In a range-finding study in rats (Clemens *et al*., 1990), 14/15 pups from one litter of the high-dose group showed malformations. These were not clearly associated with maternal toxicity, since the body weight gains of the two next lower dose groups were more affected than those of the high-dose group, but without any malformations in the pups. However, since only one litter was affected, the toxicological significance of this finding remains unclear. An increased incidence of extra ribs was not recorded in the rabbit studies. The skeletal anomalies in the form of abnormal or incomplete ossification that occurred in one study (Becker *et al*., 1987b) were likely to have been a manifestation of developmental delay, attributed to the maternal toxicity and are, additionally, common in rabbits.

Exposure to triadimenol resulted in increases in placental weight in two rat studies (Clemens *et al*., 1990; Renhof, 1984) and one rabbit study (Clemens *et al*., 1992). The study authors stated that this is an effect that is commonly seen with azole-containing substances. The finding is of uncertain significance, but a hormonal effect cannot be excluded.

4.11.2.2 Human information

No information available.

4.11.3 Other relevant information

In a dominant lethal assay (section 4.9), a single dose of 500 mg/kg/d had no effect on male fertility.

4.11.4 Summary and discussion of reproductive toxicity

4.11.4.1 Fertility

The reproductive toxicity of triadimenol has been investigated in oral studies in rats and rabbits.

Both multi-generation studies showed an increase in the severity of the fertility effects through the generations, so that all dose groups were affected by the final generation. The toxicokinetic investigations (section 4.1) indicated that excretion reached approximately 80%-90% of an administered single or repeated dose at 24 hours, so it is possible that bioaccumulation of triadimenol occurs.

In these two studies, parental toxicity as exhibited by decreased body weight gains, which also worsened through the generations, was evident but there were no overt clinical symptoms. The effects on fertility were more marked when higher doses (60 & 240 mg/kg/d) were administered, but were still evident at the F_1 first and second matings when lower doses were used (from 1.8 mg/kg/d), and in the F_{3B} generation in the low-dose (15 mg/kg/d) group, when parental toxicity was slight or absent. The insemination index was also reduced in the one study where this parameter was investigated. The reduced fertility index in these studies is not regarded as being a non-specific secondary consequence of parental toxicity. No specific investigations have determined if the possible effect on fertility is mediated through males or females, although male fertility was not affected by a single dose of triadimenol in a dominant lethal assay.

4.11.4.2 Developmental toxicity

When triadimenol was administered just during gestation, post-implantation losses only occurred at higher doses (from 120 mg/kg/d in rats and 200 mg/kg/d in rabbits) and in association with maternal toxicity. Continuous administration of triadimenol in a multi-generation study resulted in statistically significantly reduced total litter sizes from 60 mg/kg/d; it is not known if it was pre- or post-implantation losses that were most affected. However, this effect on litter sizes was associated with quite severe maternal toxicity. Differences in pup viability and body weight were also likely to be due to maternal toxicity (at the higher doses) or chance (at the lower doses), and are not sufficiently convincing to justify classification.

The increased incidences of supernumerary ribs occurred in two rat studies in dose-response relationships, but were only statistically significantly increased or clearly above the control value when maternal toxicity was evident. Uncertainty surrounds the developmental/teratogenic

significance of supernumerary ribs, in particular their post-natal reversibility or otherwise. The presence of supernumerary ribs that are small in size may be considered to be less significant with respect to teratogenic potential than ribs that are more than half the size of a full rib, which are considered to be more likely to persist post-natally. Generally, findings of this nature are not used as evidence for classification. Supernumerary ribs did not occur in rabbits when triadimenol was administered in relatively high doses that resulted in quite severe maternal toxicity.

In one rat study, one litter of the high-dose group contained a large number of foetuses with malformations, including cleft palate. However, the fact that they occurred only in one litter seems to provide less evidence of a specific developmental effect than if they had been distributed amongst several litters; one explanation may be that there was a genetic link to one of the parents.

4.11.5 Comparison with criteria

The developmental toxicity observed was generally associated with maternal toxicity and did not provide evidence of a specific effect. Likewise, reduced post-natal survival and weight gain occurred together with maternal toxicity and/or reduced pup birth weight. There was therefore insufficient evidence to propose a classification for developmental toxicity or effects on or via lactation. However, triadimenol reduced fertility in a multi-generation study in rats, with supportive evidence provided by a two-generation study in rats that used lower doses; this effect did not appear to be a secondary effect of non-specific toxicity. Classification for these effects is therefore indicated.

There is no human data available, so category 1A (CLP) is not appropriate.

In deciding if category 1B or 2 is the more appropriate, several factors are taken into consideration; these include the specificity of the effect and any association with parental toxicity; mechanistic information that indicates the effects may not be relevant for humans; the strength of the evidence; deficiencies in the study that make the quality of the evidence less convincing.

There was no mechanistic information to inform on the relevance of the findings to humans. Thus, they are regarded as being of relevance to humans.

In terms of the multi- and two-generation studies, both of these had deficiencies that reduced their quality and the information available from them. There was no information on whether the effect on fertility was mediated through the males or the females. Given the weaknesses in both studies, together with only one species (rat) having been investigated, the fact that a clear dose-response was not always obtained, with no gross or histopathological evidence of damage to the reproductive organs, category 2 (CLP) is considered to be more appropriate for the fertility effects (Repro. Tox. Cat. 3; R62 under Directive 67/548/EEC).

4.11.6 Conclusions on classification and labelling

CLP Regulation:	**Propose Repr Cat 2; H361f**
Directive 67/548/EEC:	**Propose Repro. Cat. 3; R62**

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Information on acute neurotoxicity is presented in section 4.3 on STOT-SE. There are no available studies on the repeated-dose neurotoxicity of triadimenol.

4.12.1.2 Immunotoxicity

No information available.

4.12.1.3 Specific investigations: other studies

No information available.

4.12.1.4 Human information

No information available.

4.12.2 Summary and discussion

4.12.3 Comparison with criteria

4.12.4 Conclusions on classification and labelling

5 ENVIRONMENTAL HAZARD ASSESSMENT

Triadimenol exists as two diastereomers, referred to as A and B. Some environmental studies were able to differentiate between the isomers, but others could not. The two environmental simulation studies do have measurements of A:B, and slight differences were noted in the ratios at the end of the tests. The Draft Assessment Report (DAR) produced under Directive 91/414/EEC concluded the differences were not of practical concern for environmental exposure or the risk assessment. The active substance was therefore considered as the sum of the isomers..

5.1 Degradation

Table 21: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Not specified	Hydrolysis T1/2 > one year	Hydrolytically stable	Nicholls & Thornton, 1980
EPA 161-2	Aqueous photolysis T1/2 = 9 days	Not rapidly photodegradable	Brumhard and Sneikus, 2002
Not specified	Water-sediment whole system DT50 > 377 days	Indicates *not readily biodegradable*	Anderson, 1986, revised 2002; Schäfer, 2002

5.1.1 Stability

A hydrolysis study using radio-labelled triadimenol was run at pH 4.5, 7.1 and 9.2 at 20 and 40°C for 32 days. The half-life of triadimenol at 20°C was estimated as above one year at all pHs. Due to the age of the study, this was not to GLP or a specific test guideline. (DAR reference: Nicholls & Thornton, 1980)

Three aqueous photolysis studies are available. The most modern was conducted using radio-labelled triadimenol with high chemical purity (>99% pure) and carried out according to EPA guideline 161-2. The test was run for 12 days and used a xenon lamp filtered to exclude wavelengths below 290 nm. Under sterile experimental conditions of continuous illumination, triadimenol degraded with a mean first order DT50 of 9 days. This was considered by the study authors to be equivalent to an environmental half-life of 48 summer days (June) in Athens, Greece (38.03˚N). It was also found that triadimenol only exhibited very limited adsorption of light in the range 290 – 292 nm. No individual metabolites ≥10% applied radioactivity (AR) were observed to occur. (DAR reference: Brumhard and Sneikus, 2002)

A second study using 96.7% purity triadimenol was considered invalid due to photosensitising impurities in the test solutions. The third study determined a DT50 of 1.7 days under artificial light; however due to its age few details are available for the study, for example the light source. This means that the study is of limited use.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

No estimation of biodegradation was made in the DAR.

5.1.2.2 Screening tests

There is no ready biodegradation study available for this substance, and the notifier proposed that the substance is not readily biodegradable.

5.1.2.3 Simulation tests

An aerobic water/sediment simulation study using radio-labelled triadimenol is available. It was conducted prior to both GLP and a specific test guideline being available. The study was run for 13 weeks at 22°C using two systems, a freshwater sediment (from a drainage ditch of a fruit orchard) and a pond sediment (from a recultivated gravel pit). Samples were taken for analysis in weeks 0, 2.5, 5, 9 and 13.

Mineralisation was relatively low, with 2.8 – 3.8% AR at the end of the test, which supports the assumption of not readily biodegradable. Only two metabolites were identified, triadimefon and M02 (see soil degradation below for structures). The maximum occurrence of triadimefon was 0.7% AR in sediment at 5 weeks after treatment; the maximum occurrence of M02 was 1.7% in water at 13 weeks after treatment. This indicates that little degradation of the parent substance had occurred by the end of the test. The formation of unextracted residues was relatively low, being 0.6 – 2.6% AR at the end of the study.

The study indicated relatively high levels of partitioning of triadimenol to sediment, particularly in the system with higher organic carbon content in sediment. In this system, 52.3% AR was found as triadimenol in sediment at 2.5 weeks after treatment. The fate of the two isomers was similar in both systems. There was a slight change in the isomer ratio during the study but this was not considered to have any practical impact in the DAR. Dissipation from the water phase in both systems could not be calculated with any degree of reliability with first order kinetics. This was explained by water phase kinetics being dominated by partitioning into sediment in both systems. Although there was no calculation of actual degradation rates in water, the results of the sediment/water study were interpreted as indicating that true degradation in this study was likely to be slow, and possibly little different from the slow degradation seen in the aqueous hydrolysis study.

There was some criticism in the DAR of the limited number of samples taken in the study (five) and the location of the radio-labelling in the phenyl ring (the issue being that a third potential metabolite, M04, 1, 2 4-triazole would not be detected). However, given the slow degradation of triadimenol, very low metabolite formation and that identified metabolites all retained the triazole ring, the DAR indicates that it is unlikely that M04 would have been formed in significant quantities in the study. Overall the study was *considered useful for regulatory decision making* in the DAR. (DAR reference: Anderson, 1986, revised 2002)

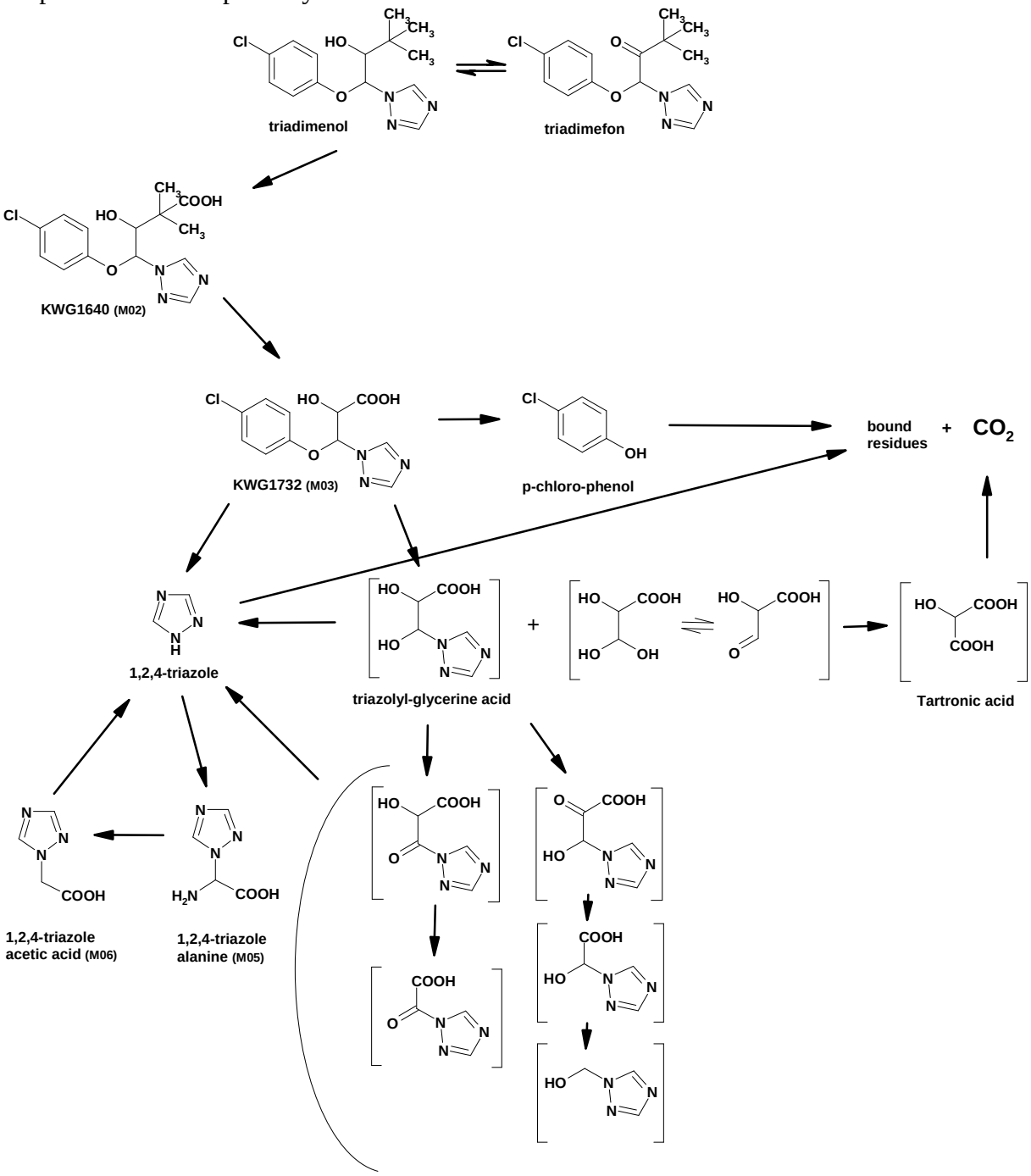
Later work (DAR reference: Schäfer, 2002) to calculate DT50s at 20°C from the above study determined total system DT50s as 443 and 377 days for the freshwater and pond sediment systems respectively.

Two aerobic soil degradation studies are available. The first study was run according to BBA guidelines IV, 4-1, 1986 and to GLP. It used radio-labelled triadimenol (containing an isomeric ratio A:B of 55:45) applied to four different soils (two silty loams, a sandy loam and a loamy sand). The study was run for 100 days in the dark at 20°C with samples taken on days 0, 3, 7, 14, 28, 49/56, 77 and 100. The ratio of isomers A:B was found to decline gradually in soils with the greatest ability to degrade total triadimenol most quickly (ratio at 100 days: 35:50). In soils with the least ability to degrade total triadimenol, the isomer ratio remained virtually unchanged over time

(i.e. 55:45). DT50s for the different soils were calculated as being between 47.3 and 362 days. (DAR reference: Brumhard, 2003). The second study was conducted according to BBA leaflet no. 36 (1973) and used two BBA standard soils 1 and 2. There are only brief details of this non-GLP study. It was run for 180 days at 22°C using cold triadimenol. The calculated DT50s normalised to 20°C were 134 and 349 days. (DAR reference: Voegeler, 1976).

The DAR proposes the metabolic pathway for triadimenol in aerobic soil below.

Proposed metabolic pathway for triadimenol in aerobic soil



Triadimefon = M01; KWG1640 = M02; 1,2,4-triazole = M04; p-chloro-phenol = M07

5.1.3 Summary and discussion of degradation

Triadimenol was found to be stable to hydrolysis. Rapid photolysis was not observed in the laboratory studies. A ready biodegradation study is not available, but no rapid biodegradation was indicated in the water/sediment or the soil degradation studies. Overall there is good evidence that the substance is not rapidly biodegraded, and therefore an assumption of *not readily biodegradable* is reasonable. Due to the stability and lack biodegradation, the environmental classification of the substance should be made using the properties of the parent substance.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

The adsorption of triadimenol was described by three separate studies covering a total of 14 soils. Two of the studies pre-dated requirements for GLP compliance but were considered relatively well reported and the adsorption coefficients derived to be reliable. In spite of the large number of soils tested, the range of pH encompassed did not cover alkaline soils. The notifier has addressed this, considering that the molecule is in a non-ionised state between pH 3-10, and would not be expected to show any particular pH related dependency at environmentally relevant pH. A wide range of other soil properties was considered. There is no obvious trend between pH and Koc in the experimental data.

Koc values were between 108 and 702 ml/g. The arithmetic mean and the median of the values were both 273. (DAR reference: Vogeler, 1978; Puhl and Hurley, 1978, revised 1983; Hein, 2002)

5.2.2 Volatilisation

The DAR states that triadimenol has a vapour pressure of 6×10^{-7} and 4×10^{-7} Pa (diastereomers A and B respectively) at 20˚C and Henry's Law Constant of 3×10^{-6} and 4×10^{-6} Pa.m3/mole (diastereomers A and B respectively). It is therefore not considered volatile. (Webber & Krohn, 1996)

5.2.3 Distribution modelling

Not relevant to classification.

5.3 Aquatic Bioaccumulation

Table 22: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
EPA-FIFRA 72-6	BCF = 21 l/kg		Forbis, 1987

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

The substance has a log K_{ow} between 3.08 and 3.28, which implies a moderate bioaccumulation potential. No other data are available.

5.3.1.2 Measured bioaccumulation data

A fish bioaccumulation study with radio-labelled triadimenol (99% radiochemical purity) was run according to EPA-FIFRA 72-6 and GLP. This used bluegill sunfish (*Lepomis macrochirus*) and was conducted under flow-through conditions. The uptake period was 28 days and the depuration period was 14 days. One test concentration of 0.97 mg a.s./l with dimethyl formamide (DMF) solvent was used. The concentration of DMF was not indicated in the DAR. A control, also using DMF, was run in parallel. The uptake phase was initiated by transferring 125 acclimatised fish into each of the control and test chambers (two chambers per treatment). Fish were sampled on days 1, 3, 7, 14, 21

and 28 of the uptake phase and days 0, 0.17, 1, 3, 7, 10 and 14 of the depuration phases of the study. No treatment-related mortality or adverse effects on the fish were noted and environmental parameters were within acceptable limits throughout the study.

The time to reach 90% of steady-state was 1.4 days. The daily bioconcentration factors of triadimenol ranged from 7.1 to 27 for whole fish, 11 to 44 for visceral portions and 1.9 – 5.4 for edible portions. When moved to clean water, residues of triadimenol depurated with a half-life of 0.42 days. After 14 days in clean water 99% of the mean plateau radioactivity was depurated from whole fish and a whole fish BCF of 21 was estimated. No mention of lipid measurement is made in the DAR. (DAR reference: Forbis, 1987).

A 42-day flow-through fish bioaccumulation study using *Lepomis macrochirus* is available for the metabolite triadimefon. This determined a whole fish BCF of 64.

5.3.2 Summary and discussion of aquatic bioaccumulation

Measured data suggests Triadimenol does not bioaccumulate significantly. The BCF value of 21 is lower than the trigger values for either Directive 67/548/EEC or Regulation EC 1272/2008.

5.4 Aquatic toxicity

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Three 96-h acute fish tests are available. Nominal concentrations were used to calculate the results as measured concentrations were indicated to have been maintained at >80% in all the tests. In addition a prolonged fish toxicity study is also available.

Table 23: short-term toxicity to fish

Purity	Species	Test Guideline	Endpoint	Toxicity value in mg/l of a.s.	conditions	ref
96.3%	Rainbow trout *Oncorhynchus mykiss*	OECD 203	96-h LC50 96-h NOEC	21.3 6.25 (nominal concentrations)	Static	Dorgerloh (1993a)
94.9%	Golden orfe *Leuciscus idus*	n/a	96-h LC50 96-h NOEC	17.4 <15 (nominal concentrations)	Static	Hermann (1979)
96.3%	Golden orfe *Leuciscus idus*	OECD 203	96-h LC50 96-h NOEC	27.3 6.25 (nominal concentrations)	Static	Dorgerloh (1993b)
96.3%	Rainbow trout Oncorhynchus mykiss	OECD 204	28-day LC50 28-day NOEC	11.4 3.13 (mean-	Semi-static	Dorgerloh (1993)

				measured concentration)		

The Golden Orfe test (Hermann, 1979) has the lowest 96-h LC50 of 17.4 mg/l. This is an old non-GLP study and was not stated as being run to a specific test guideline. The fish loading appears to exceed the current guideline at some concentrations, and different numbers of animals appear to have been used for different concentrations (between 10 and 30). Nominal concentrations of 0, 15, 16, 17, 17.35, 17.70, 18.4, 19.2 and 20 mg a.i./l were run, with acetone used as an adjuvant (concentration not stated). During the test no effects were observed in the control fish. No mortality was observed in the lowest concentration, although sub-lethal effects were seen. The 96-h LC50 based on nominal concentrations was 17.4 mg a.i./l. The report is relatively concise and some minor information is missing, such as pH and light/dark cycle. However it was stated that oxygen levels were maintained above 7 mg O_2/l. Concentration measurements were made in a separate aquarium that did not contain fish. These indicated that the substance was stable during the test period (>80% between 2 and 96 hours). Comparison with measured concentrations in the other two (GLP compliant) acute fish studies indicated that the test substance was also stable in the presence of fish during the test period (mean-measured concentrations > 80% nominal). Together it seems reasonable to assume that the test substance was stable in the earlier test in the presence of fish, and therefore the reporting of the results as nominal concentrations is acceptable.

Overall while the test has some weaknesses, it is in line with the other fish results, including one conducted on the same species. The purity of triadimenol in the earlier test is slightly lower than the later studies, however again the results are similar for all three tests, so the purity does not appear to have affected the outcome of the tests.

An OECD 204 prolonged fish toxicity study was run for 28 days under semi-static conditions using *Oncorhynchus mykiss*. This used 96.3% purity triadimenol. Fish were hatched at the test facility and held for at least 14 days prior to test commencement. At the beginning of the test mean body weight of the fish was 2.9 g and mean body length was 6.2 cm. Nominal concentrations were 3.13, 6.25, 12.5, 25.0 and 50.0 mg/l. Mean-measured results were LC50 = 11.4mg/l and NOEC = 3.13mg/l. 100% mortality was observed at 25.0 and 50.0mg/l. The study was GLP compliant. (DAR reference: Dorgerloh, 1993)

Tests for degradants:

Triadimefon: *Oncorhynchus mykiss*: 96-h LC50 4.08 mg/l, NOEC 0.71 mg/l

Triadimefon: *Lepomis macrochirus*: 96-h LC50 10.0 mg/l NOEC 3.50 mg/l

M04: *Oncorhynchus mykiss*: 96-h LC50 760 mg/l NOEC 100 mg/l

5.4.1.2 Long-term toxicity to fish

The possibility of endocrine disruption was raised during the peer review of the DAR. However as ED is not included as a requirement under 91/414/EC, any ED assessment was agreed as a matter for individual Member States. Following discussions between the registrant and the German authorities, the registrant was to conduct a FELS test and a 21-day fish screening assay (FSA) under national regulations. The UK CA has received the FELS test but not the FSA data.

As part of the 3rd stage of the EU review process a need for endocrine disruption (ED) characterisation was highlighted for the group of specific fungicides including triadimenol. All the

substances were given the following confirmatory data requirement: 'further information addressing the potential endocrine disrupting properties of [active substance] within two years after the adoption of the OECD test guidelines on endocrine disruption or, alternatively, of Community agreed test guidelines'.

The UK CA does not expect to receive any ED testing for triadimenol under the 3rd stage for at least two years. The environmental classification could be reviewed again once these data are available,

Table 24: long-term toxicity to fish

Purity	Species	Test Guideline	Endpoint	Toxicity value in mg/l of a.s.	conditions	ref
99.2%	Fathead minnow *Pimephales promelas*	OECD 210	35-day NOEC (growth)	0.17 (mean-measured concentration)	Flow-through	Nieden & Lam (2007)

Early life stage toxicity of triadimenol to *Pimephales promelas* (Nieden & Lam, 2007)

Subsequent to the submission of the DAR the notifier has provided a FELS test using *Pimephales promelas* to the UK CA. These data are not included in the DAR. This test was conducted using 99.2% purity triadimenol. Newly fertilised eggs were exposed to mean measured concentrations of 0.05, 0.10, 0.17, 0.38, 0.75, 1.69 and 3.23 mg a.i./l dispersed in diluent water using acetone (l00µl/l). Control and solvent controls were also run. Four replicates per level were run, with 35 eggs per replicate, which were thinned to 20 alevin after the hatching phase. The test was conducted at 25°C (± 1°C) under flow-through conditions.

Hatching was completed five days after initiation of the study (designated day 0 post-hatch). There was no significant difference between controls and the other treatments. There was also no difference for alevin survival (measured at day 5), but fry survival was lower for the top two concentrations (measured at day 35). Impacts on growth were also seen for the higher concentrations. The most sensitive end point was growth (weight) with a mean-measured NOEC of 0.17 mg a.i./l. Environmental parameters were within acceptable limits throughout the study. The study was undertaken according to OECD 210 and was GLP compliant.

Degradants:

Triadimefon: 35-day FELS test using *Pimephales promelas* NOEC (growth – length/weight): 0.17 mg/l

M04 (1, 2, 4-triazole): 28-day fish juvenile growth test using *Oncorhynchus mykiss*: NOErC ≥ 100 mg/l

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

One acute invertebrate study is available, and is indicated to be GLP compliant. This was conducted to OECD 202 using *Daphnia magna* and under static conditions. It used 96.6% purity triadimenol and determined a 48-h EC50 of 51 mg/l and a NOEC of 10 mg/l. Results were based on nominal

concentrations. Mean-measured concentrations were only available for the lowest dose, which suggested that the test solutions were stable. (DAR reference: Heimbach, 1989)

Degradants:

Triadimefon: *Daphnia magna* 48-h EC50 7.16 mg/l, NOEC 2.35 mg/l

M04 (1, 2, 4-triazole): *Daphnia magna* 48-h EC50 >100 mg/l, NOEC 100 mg/l

M04 (1, 2, 4-triazole): *Daphnia magna* 24-h EC50 800 mg/l (graphic estimation), NOEC 320 mg/l

5.4.2.2 Long-term toxicity to aquatic invertebrates

Table 25: long-term toxicity to aquatic invertebrates

Purity	Species	Test Guideline	Endpoint	Toxicity value in mg a.i./l	conditions	ref
92%	*Daphnia magna*	n/a	21-day NOEC (reproduction) 21-day NOEC (mortality)	0.199 0.145 (mean-measured concentration)	Flow-through	Lamb, 1982
97.3%	*Daphnia magna*	OECD 211	21-day NOEC (reproduction) 21-day NOEC (mortality)	1.25 n.d. (mean-measured concentration)	Semi-static	Dorgerloh & Sommer, 2001
96.9%	*Chironomus riparius*	BBA (1995)	28-day NOEC (development & emergence)	≥ 0.1 (initial concentration)	Static	Heimbach, 1998

Long-term toxicity of triadimenol to *Daphnia magna* (Lamb, 1982)

In a non-GLP study the toxicity of triadimenol (purity: 92%) to *Daphnia magna* was investigated over a period of 21 days in a flow-through system. The study was not conducted to any recognised protocol, but generally it appears to have been conducted and reported in line with the principles of OECD 211. It used nominal concentrations of 0.050, 0.100, 0.200, 0.400, 0.800 mg a.i./l and a control. Two replicates were run at each level, with 15 animals per replicate. The daphnids were fed twice daily, and environmental parameters were within acceptable limits throughout the study. The mean concentrations of triadimenol in the test chambers ranged from 100 to 145% of the nominal concentrations.

Sub-lethal effects (loss of equilibrium) were observed at 24 and 48 hours in the 0.400 and 0.800 mg a.i./l levels. No sub-lethal effects were observed after 48 hours. There was no mortality at the two lowest concentrations tested but there was 100% mortality at the highest concentration tested. The control group appeared normal throughout the 21 days of exposure. There were no significant differences in the number of young produced in the 0.050 and 0.100 mg a.i./l concentrations compared to the young produced in the control. Even though there was 50% mortality in the 0.200 mg a.i./l level, the daphnia produced approximately the same number of young per surviving adult as the control group. There were no young produced at 0.800 mg a.i./l, and reproduction was

reduced by approximately 56% among daphnia at 0.400 mg a.i./l. The mean-measured NOEC for reproduction was 0.199 mg a.i./l, and mean measured NOEC for mortality was 0.145 mg a.i./l.

Long-term toxicity of triadimenol to *Daphnia magna* (Dorgerloh & Sommer, 2001)

A second GLP study was run according to OECD 211 and US EPA 72-4 using 97.3% triadimenol using static renewal conditions (renewal every 48-72 hours). Nominal test concentrations of 0.04, 0.08, 0.16, 0.32, 0.64, 1.28 and 2.56 mg a.i./l were run as well as a control and a solvent (DMF) control. DMF solvent was used at 100 µl/l. There were ten test vessels per concentration with one test animal per vessel. The study was run for 21 days with test solutions renewed every 48 hours during the week and at 72 hours over weekends. The test organisms were fed (daily, except for the first weekend of the study), but the test solutions were not aerated during the study. Light intensity was indicated to be about 1500 lux and water quality was indicated to be within the guideline recommendations. Measured concentrations of the test solutions were between 83% and 116% of nominal. Little difference in the measurements of fresh and expired concentrations was observed.

Statistically significant mortality (>20%) was not observed in any test level and the controls. Similarly there was no statistical difference between the body length of the controls and the animals at any test level, and so the NOEC for the body length of the parent animals was 2.56 mg as/l. For reproduction, statistically significant effects were observed at 2.56 mg a.s./l, and the NOEC for reproduction was 1.28 mg a.s./l.

Long-term toxicity of triadimenol to *Chironomus riparius* (Heimbach, 1998)

A GLP compliant study was conducted in accordance with BBA (1995) method, the effect of technical triadimenol (purity: 96.9%) on the development and emergence of *Chironomus riparius* larvae in a sediment/water system was investigated. This was run using a single test concentration of 0.1 mg a.s./l and a control. 25 animals were used for each replicate and four biological replicates were run for each level. In addition one replicate was run for each level for analytical purposes. Water quality parameters for control and treatment replicates were within levels permitted under the test guideline. Measured concentrations of the test water during the study showed these declined from 100% of nominal at one hour, 80% on day 7 to 57% on day 28. Analysis of the pore water detected at triadimenol at 3.9% on day 7 and 2.9% on day 28. The DAR concluded these findings suggested a small amount of the test substance adsorbed to the sediment and/or was degraded during the study.

The number of emerged midges was not significantly different to the control at the test concentration of 0.1 mg a.s./l, and neither was the development rate. Therefore the NOEC for both development and emergence was 0.1 mg a.s./l (initial concentration), the highest concentration tested.

Degradants:

Triadimefon: *Daphnia magna* – 21-day non-GLP NOEC (mortality) 0.100 mg/l

Triadimefon: *Daphnia magna* – 21-day NOEC (growth) 0.052 mg/l

5.4.3 Algae and aquatic plants

One algal study is available. This was conducted to OECD 201 using *Pseudokirchneriella subcapitata* and 97.3% purity triadimenol. The 72-h ErC50 was 38 mg/l, and the NOErC was 4.7 mg/l. Results were based on nominal concentrations as measurements indicated levels were maintained at >80% of initial concentrations throughout the test. The study was GLP compliant. (DAR reference: Scheerbaum, 2001)

Degradants:

Triadimefon: *Pseudokirchneriella subcapitata:* 120-h ErC50 2.01 mg/l, NOErC 1.20 mg/l

M04 (1, 2, 4-triazole): *Pseudokirchneriella subcapitata:* 72-h ErC50 >31 mg/l, NOErC 3.1 mg/l

5.4.4 Other aquatic organisms (including sediment)

None

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

A ready biodegradation study is not available. The substance is hydrolytically stable and not rapidly photodegraded. Data from long-term degradation studies in water-sediment systems and soil do not indicated rapid primary degradation or mineralisation. On this basis it is concluded the substance should not be classified as readily biodegradable or rapidly degradable. The BCF value of triadimenol is 21, which is lower than the trigger values for either Directive 67/548/EEC or Regulation EC 1272/2008.

The ecotoxicity test results suggest the substance exhibits acute aquatic toxicity between 10-100 mg/l. This is consistent across all three trophic levels tested. The results indicate that fish are the most sensitive taxa, with all three acute fish test results lower than the *Daphnia* and algal results. The most sensitive acute endpoint is a 96-h LC50 = 17.4 mg a.i./l (nominal concentration) for *Leuciscus idus*. Whilst the result from this non-GLP test should be treated with caution, it is in agreement with the other two fish test results.

The long-term aquatic data suggest toxicity in the range 0.1-1 mg/l. Fish are the most sensitive taxa, based on the recently submitted FELS study. The non-GLP 21-day *Daphnia* study also has results in this range (albeit using lower purity test substance), but the more modern 21-day *Daphnia* study using a purer test substance found a higher NOEC (1.28 mg/l). No effects were observed in the *Chironomid* study, and so a true NOEC cannot be derived from this limit test. The growth NOEC for algae was 4.7 mg/l indicating that aquatic plants are not the most sensitive trophic level. Under the 2nd ATP of the CLP Regulation, using the chronic ecotoxicity criteria, triadimenol fulfils the criteria for aquatic environmental hazard chronic category 2. This is using the 35-day growth NOEC of 0.17 mg/l (mean-measured) from the FELS test using *Pimephales promelas*.

One of the degradants of triadimenol (triadimefon) appears to be more ecotoxic than the parent substance, but the rate of its formation appears to be very slow from the environmental simulation studies. Therefore the classification should be based on parent substance.

CLP Regulation:	**Aquatic chronic 2; H411**
Directive 67/548/EEC:	**N; R52/53**

Note that under the 2nd ATP of the CLP Regulation, using the chronic ecotoxicity criteria, triadimenol fulfils the criteria for aquatic environmental hazard chronic category 2. This is using the 35-day growth NOEC of 0.17 mg/l (mean-measured) from the FELS test on Pimephales promelas. No M factor is required.

6 OTHER INFORMATION

This substance has been reviewed by the United Kingdom Competent Authority under Council Directive 91/414/EEC. The studies evaluated in this dossier were largely taken from the draft assessment report produced under this review programme, although additional information was obtained from studies submitted by the Notifier after the assessment report had been published. A search of the publicly-available literature did not reveal any additional information relevant for inclusion in this report.

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