CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

1,2,4-triazole

EC Number: **206-022-9**

CAS Number: **288-88-0**

Index Number: **613-111-00-X**

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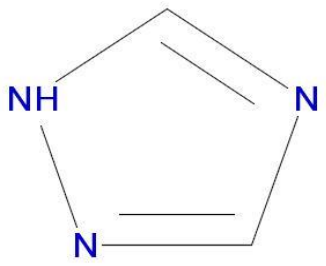
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	1H-1,2,4-triazole
Other names (usual name, trade name, abbreviation)	1,2,4-triazole
ISO common name (if available and appropriate)	/
EC number (if available and appropriate)	206-022-9
EC name (if available and appropriate)	1,2,4-triazole
CAS number (if available)	288-88-0
Other identity code (if available)	/
Molecular formula	C2H3N3
Structural formula	
SMILES notation (if available)	N1C=NC=N1
Molecular weight or molecular weight range	69.0653
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	NA
Description of the manufacturing process and identity of the source (for UVCB substances only)	NA
Degree of purity (%) (if relevant for the entry in Annex VI)	≥ 99.5%(W/W)

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
1,2,4-triazole (EC n° 206-022-9)	≥ 99.5%(W/W)	Acute Tox. 4*, H302 Eye Irrit.2, H319 Repr.2, H316d***	Acute Tox. 4, H302 Eye Irrit.2, H319 Repr.2, H316d***

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
No impurities present at ≥0.3% W/W which contribute to the classification of the substance Confidential				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
No additives					

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
1,2,4-triazole (EC n° 206-022-9)	94.0% (W/W)	Not relevant for classification		Embryotic study performed in rats (Renhof M., 1988a)
1,2,4-triazole (EC n° 206-022-9)	95.3%(W/W)	Not relevant for classification		Embryotic study performed in rats (Renhof M., 1988b)
1,2,4-triazole (EC n° 206-022-9)	No information available	Not relevant for classification		-Deveopmental toxicity study in rats (Wickramaratne, 1987) -Subacute toxicity (30d) in rats (Anonymous, cited in US EPA memorandum, 2006)
1,2,4-triazole (EC n° 206-	98.5%(W/W)	Not relevant for classification		Chronic toxicity study (12 months)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
022-9)				**in rats (Wahle B.S., 2010)**
1,2,4-triazole (EC n° 206-022-9)	**≥ 99.5%(W/W)**	**Not relevant for classification**		**All other studies in section 10.10**

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	613-111-00-X	1,2,4-triazole	206-022-9	288-88-0	Acute Tox. 4* Eye Irrit.2 Repr.2	H302 H319 H361d***	GHS08 GHS07 Wng				
Dossier submitters proposal	613-111-00-X	1,2,4-triazole	206-022-9	288-88-0	**modify to** Acute Tox. 4 **Repr. 1B**	 H302 H360FD	GHS08 GHS07 Dgr				
Resulting Annex VI entry if agreed by RAC and COM	613-111-00-X	1,2,4-triazole	206-022-9	288-88-0	Acute Tox. 4 Eye Irrit.2 Repr.1B	H302 H319 H360FD	GHS08 GHS07 Dgr				

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Data conclusive but not sufficient for classification	No
Flammable gases (including chemically unstable gases)	Data conclusive but not sufficient for classification	No
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Data conclusive but not sufficient for classification	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Data conclusive but not sufficient for classification	No
Self-reactive substances	Data conclusive but not sufficient for classification	No
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Data conclusive but not sufficient for classification	No
Self-heating substances	Data conclusive but not sufficient for classification	No
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	No
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Data conclusive but not sufficient for classification	No
Organic peroxides	Data conclusive but not sufficient for classification	No
Corrosive to metals	Data lacking	No
Acute toxicity via oral route	Acute tox. 4, H302	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	No
Acute toxicity via inhalation route	Data lacking	No
Skin corrosion/irritation	Data conclusive but not sufficient for classification	No
Serious eye damage/eye irritation	Eye Irrit. 2, H319	No
Respiratory sensitisation	Data Lacking	No
Skin sensitisation	Data conclusive but not sufficient for classification	No
Germ cell mutagenicity	Data conclusive but not sufficient for classification	No
Carcinogenicity	Data lacking	No
Reproductive toxicity	Repr.1B, H360FD	Yes
Specific target organ toxicity-single exposure	Data conclusive but not sufficient for classification	No
Specific target organ toxicity-repeated exposure	Data conclusive but not sufficient for classification	No
Aspiration hazard	Data lacking	No
Hazardous to the aquatic environment	Data conclusive but not sufficient for classification	No

Hazard class	Reason for no classification	Within the scope of public consultation
Hazardous to the ozone layer	Data lacking	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The DSD classification was agreed by the TC C&L in 1996 (Dir. 67/548/EEC) :

Xn; R22
Xi; R36
Repr. Cat. 3; R63

The current CLP classification is a translation thereof and is included in annex VI (ATP00) :

Acute tox. 4*, H302
Eye Irrit. 2, H319
Repr. 2, H361d

In the meanwhile new data were generated by means of a 2-genaration study in rats following OECD 416 guideline (Young A.D. and Sheets L.P., 2005). Wistar rats were exposed via their diet to either 0, 250, 500 or 3000 ppm of 1,2,4-triazole from 10 weeks before mating to day 21 of lactation. Body weights in both sexes reduced significantly during different exposure periods. In conjunction with body weights disturbances, absolute and relative ovarian weights were significantly increased at 3000 ppm in P0 females. Furthermore, changes in the number of corpora lutea were noted. Also modifications of sperm parameters, significantly modified at 3000 ppm, were reported. Moreover for some endpoints (% of normal spz, % of detached spz) changes were also noted at a lower dose levels. In females, reproductive data changes were seen. The most important was the fertility index which was severely decreased (7.1 % at 3000 ppm vs 76.7% in control).

NOAEL (parental toxicity) : 500 ppm
NOAEL (fertility) : < 250 ppm based on the sperm parameters
NOAEL (developmental toxicity) : 500 ppm

The 2-generation study provides also clear evidence of adverse effects on fertility. Together with the histopathological findings in the testis in the subacute (Wahle B.S., 2004a) and chronic toxicity study (Wahle B.S., 2004b) a classification as Repr. 1B F is warranted.

Severe developmental disturbances (increased cleft palate, incidence of cryptorchism, increase of pre- and post-implimantation loss, increased incidence of runts) were observed in 2 developmental toxicity studies in rats (Renhof M., 1988a &1988b). Furthermore a dose-related increase in incidence of dead or resorbed conceptuses per liter was observed in rabbits (Hoberman, 2004).
Such severe effects warrant a classification as Repr. 1B D.

BE CA performed a substance evaluation on 1,2,4-triazole and the draft decision was discussed during MSC-54 (June 2016). Initially, two request for information were proposed :- the H295R Steroidogenesis Assay in vitro (OECD TG 456), and 2) an Extended One-Generation Reproductive Toxicity Study (EOGRTS; OECD TG 443) in rats, oral route with extension of cohort 2A and 2B (DNT cohorts), without extension of cohort 1B to mate the F1 animals to produce the F2 generation and without cohort 3 (DIT).
Based on the discussions during the MSC-54 it was concluded that the best way forward was the submission of a CLH dossier for reproductive toxicity, more particular Repro. 1B, H360FD. The request for steroidogenesis assay was maintained.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level.

Justification is not required (art. 36 of CLP regulation 1272/2008/EC) because the substance is toxic to reproduction and new data require a change in the existing entry.

5 IDENTIFIED USES

use as interemediate

use as fertilizer

6 DATA SOURCES

REACH registration dossier

JMPR, 2008, Triazole fungicide metabolites (1,2,4-triazole; triazole alanine; triazole acetic acid), 437-490

US EPA memorandum, 2006, 1,2,4-Triazole, Triazole Alanine, Triazole Acetic Acid: Human Health Aggregate Risk Assessment in Support of Reregistration and Registration Actions for Triazole-derivative Fungicide Compounds, 1-94.

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid at 20°C and 1013 hPa	IUCLID Dataset Substance, 2000	experimental study
Melting/freezing point	120-121°C	O'Neil MJ, 2006	experimental study
Boiling point	decomposed before boiling at 260°C (at 1013 hPa)	O'Neil MJ, 2006	
Relative density	1.13g/cm^3 (1130g/L) at 153°C and 1.39 g/cm^3 at 20°C	P. Jimenez, 1989	Literature data
Vapour pressure	0.22 Pa at 20°C 80.4 Pa at 25°C	Unnamed, 2001 Unnamed, 2009	OECD TG 104 (effusion method vapour pressure balance) EPI Suite estimation
Surface tension	na		
Water solubility	730 g/L at 25°C 4244 g/L at 25°C	Vlasov O. N., Sukhovs S.I., 1988	OECD TG 105 (water solubility: flask method) EPI Suite estimation
Partition coefficient n-octanol/water	25° C, pH 5: log Pow = -0.62 25°C, pH 7: log Pow = -0.71 25° C, pH 9: log Pow = -	Unnamed, 2005	OECD TG 107 (flask shaking method)

Property	Value	Reference	Comment (e.g. measured or estimated)
	0.68 -0.58.	Unnamed, 2010	EPI Suite stimation
Flash point	139.1 °C	Unnamed, 2009	QSAR estimation
Flammability	The test substance melted when approached by the ignition flame. The substance did not burn down or burn up.	Unnamed 2010	EU Method A.10 (Flammability - Solids)
Explosive properties	Non explosive	Unnamed 2010	EU Method A.14 (Explosive properties)
Self-ignition temperature	Doesn't need to be conducted for solids with malting point <160°C		
Oxidising properties	Non oxidising : substance does not contain oxygen, fluorine or chlorine		
Granulometry	no particles smaller than 78µm	Unnamed, 2011	OECD Guideline 110 -ISO 13317-2 (Fixed Pipette Method)
Stability in organic solvents and identity of relevant degradation products	Data waiving justified based on experience in handling and use of 1,2,4-triazole		
Dissociation constant	pKA =10.00 at 22°C	Unnamed, 2011	OECD Guideline 112 (Dissociation Constants in Water)
Viscosity	study technically not feasible		

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated in this dossier.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

10.1.1 Non-human information

Table 9 : Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
Acute oral toxicity Following OECD TG 401	in rats (Wistar) 5/sex/dose	1,2,4-triazole (purity >98%) Vehicle : bi-distilled water	Oral (gavage) Doses : 1000, 1500 and 2000 mg/kg bw	LD50 : 1320.39 mg/kg	Registration dossier (study report, 1989)
Acute oral toxicity Following OECD TG 423	in rats (Wistar) 15/sex/dose	1,2,4-triazole Technically pure Vehicle : distilled water and Cremophor EL	Oral (gavage) Doses : 100 (only ♀), 250, 500, 1000 (30♂ and 15♀), 1250, 1500, 1750, 1850 (only ♂), 2000 (15♂ and 30♀) and 2500 (14♂ and 15♀) mg/kg bw	LD50 (females) : 1648 mg/kg LD50 (males) : 1650 mg/kg	Thyssen and Kimmerle, 1976. Cited in JMPR, 2008
Acute oral toxicity Following OECD TG 423	in rats (Crl:CD BR) 3 males/dose	1,2,4-triazole Purity : not specified Vehicle : methylcellulose	Oral (gavage) Doses : 500 and 5000 mg/kg bw	LD50 : >500 and <5000 mg/kg	Procopio and Hamilton, 1992. Cited in JMPR, 2008

10.1.2. Human information

No information available

10.1.3. other relevant information

No information available

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

In an acute oral toxicity study performed following the OECD guideline 401 (Registration dossier (study report, 1989)), groups of 5 male and 5 female rats were exposed by gavage to 1,2,4-triazole at a concentration of 1000, 1500 and 2000 mg/kg bw.

At the mid and high dose group, mortality was observed : in males : at 1500 mg/kg bw, 2 rats died after 24h and 2 after 48h and at 2000 mg/kg bw, 4 died after 24h and 1 after 48h and in females : at 1500 mg/kg bw, 3 rats died after 24h and 2 after 72h and at 2000 mg/kg bw, 4 died after 24h and 1 after 48h.

According to the results, the LD50 is of 1320 mg/kg bw.

In an acute oral toxicity study performed following the OECD guideline 423 (Thyssen and Kimmerle, 1976. Cited in JMPR, 2008), groups of 15 male and 15 female rats were exposed by gavage to 1,2,4-triazole at a concentration of 100 (only ♀), 250, 500, 1000 (30♂ and 15♀), 1250, 1500, 1750, 1850 (only ♂), 2000 (15♂ and 30♀) and 2500 (14♂ and 15♀) mg/kg bw.

According to the registration dossier, the LD50 for females is 1648 mg/kg bw and for males is 1650 mg/kg bw.

In an acute oral toxicity study performed following the OECD guideline 423 (Procopio and Hamilton, 1992. Cited in JMPR, 2008), groups of 3 male rats were exposed by gavage to 1,2,4-triazole at a concentration of 500 and 5000 mg/kg bw.

Mortality was observed at the high dose. At this level, all rats died within 10 minutes.

According to the results, the LD50 is of > 500 and < 5000 mg/kg bw.

10.1.2 Comparison with the CLP criteria

According to the CLP Regulation (EC 1272/2008) the classification of a substance in category 4 for oral acute toxicity is based on a LD50 between 300 and 2000 mg/kg bw.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results of the studies (Registration dossier (study report, 1989) and Thyssen and Kimmerle, 1976. Cited in JMPR, 2008), the LD50 is between 1320 and 1650. Another supporting study revealed a LD50 of > 500 and < 5000 mg/kg bw. All these obtained LD50 values fulfil the criteria for the acute toxicity in category 4.

According to all of these results, a classification as Acute Tox. 4, H302 is warranted. Based on table 3.1.1 of the CLP regulation, an ATE of 1320 mg/kg bw is warranted.

10.2 Acute toxicity - dermal route

Not evaluated in this dossier.

10.3 Acute toxicity - inhalation route

Not evaluated in this dossier.

10.4 Skin corrosion/irritation

Not evaluated in this dossier.

10.5 Serious eye damage/eye irritation

Not evaluated in this dossier.

10.6 Respiratory sensitisation

Not evaluated in this dossier.

10.7 Skin sensitisation

Not evaluated in this dossier.

10.8 Germ cell mutagenicity

Not evaluated in this dossier.

10.9 Carcinogenicity

Not evaluated in this dossier.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

10.10.1.1. Non-human information

Table 12: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
2-generation reproductive toxicity study in rats (Wistar) (30/sex/dose) Oral (diet) Following OECD TG 416 GLP	1,2,4-triazole (purity ≥99,9 %) Doses : 0, 250, 500 and 3000 ppm Exposure : through 10 weeks premating period to lactation D21 Vehicle : ethanol	No treatment-related effects were observed concerning deaths or clinical signs at any dietary dose level. Bw of males and females decreased significantly during different exposure periods (see table 13). <u>P0 :</u> Brain weight was significantly reduced at 3000 ppm in both sexes in P0. In conjunction with brain weight, degeneration/necrosis was observed in the cerebellum. Absolute and relative ovarian weights were statistically significantly increased at 3000 ppm in P0 females. Furthermore, changes in the number of corpora lutea was noted. Modification of sperm parameters observed and which were significantly modified at 3000 ppm. Moreover for some endpoints (% of normal spz, % of detached spz) changes were also modified at lower dose level. In females, reproductive data also modified. The most important was the fertility index with a severe decrease (7.1 at 3000 ppm vs 76.7% in control). NOAEL (parental toxicity) : 500 ppm NOAEL (fertility) : < 250 ppm based on the sperm parameters NOAEL (developmental toxicity) : 500 ppm	Young A.D. and Sheets L.P., 2005 (cited in JMPR, 2008)
Subacute toxicity study in mice (CD1[ICR]/BR) (15/sex/dose) Oral (feed) No OECD guideline	1,2,4-triazole (purity 99.9 %) Doses : 0, 50, 250, 500 and 2000 ppm Exposure :	No treatment-related modification of the mortality, clinical signs, bw, clinical chemistry and organ weight Histopathological evaluation : slight testicular degeneration in 5 out of 15 males at the highest dose level, minimal to slight spermatid degeneration/depletion/asynchrony, focal tubular atrophy NOAEL (males) : 500 ppm NOAEL (females) : 2000 ppm	Wahle B.S., 2004a (cited in JMPR, 2008)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
GLP	4 weeks Vehicle : ethanol		
Subacute toxicity study in rats (strain unknown) Oral Non-guideline	1,2,4-triazole (purity unknown) Doses : 0, 8, 57 and 400 mg/kg bw/d Exposure : 30-days Vehicle : unknown	At the highest dose level, a lower bw was noted and a few clinical signs were observed such as staggering, tremors and hunched posture At 57 mg/kg bw/d : slight hematological changes observed At 8 mg/kg bw/d : lower adrenal weight NOAEL : < 8 mg/kg bw/d No more information available	Anonymous (cited in US EPA memorandum, 2006)
Subchronic toxicity study in rats (Wistar) (15/sex/dose) Oral (feed) Similar to OECD TG 408 No GLP	1,2,4-triazole (purity 99.6 %) Doses : 0, 100, 500 and 2500 ppm Exposure : 3 months Vehicle : 90 % pre-mix with ultrasil VN 3	2 males and 2 females exhibited slight convulsion at 2500 ppm Terminal bw was significantly lowered at 2500 ppm. Decreased absolute testis weight at the highest dose level however no histopathological modification observed NOAEL : 500 ppm	Bomhard E. et al., 1979 (cited in JMPR, 2008)
Subchronic toxicity study in mice (CD-1[ICR]/BR) (20/sex/dose) Oral (feed) Following US EPA OPPTS 870.3100 GLP	1,2,4-triazole (purity 99.9%) Doses : 0, 500, 1000, 3000 and 6000 ppm Exposure : 90 days Vehicle : ethanol	Higher incidence of tremors at 6000 ppm A significant decrease in bw was observed in males at 3000 and 6000 ppm and at 6000 ppm in females. Brain weight was statistically modified at 6000 ppm in both sexes and at 3000 ppm in males. In conjunction with this modification, an increased incidence of Purkinje cell loss was observed at the highest dose level. Testis weight was significantly decreased at the highest dose and in conjunction, some histopathological changes were observed such as increased incidence of apoptotic like bodies, of spermatid degeneration and of tubular atrophy. Higher incidence of exfoliated germ cells and debris in the lumen of the epididymal duct at 6000 ppm. NOAEL (males) : 1000 ppm	Wahle B.S., 2004b (cited in JMPR, 2008)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		NOAEL (females) : 3000 ppm	
Combined subchronic toxicity / neurotoxicity screening study in rats (Wistar) (20/sex/dose) Oral (feed) Following OECD TG 408 and 424 GLP	1,2,4-triazole (purity 99.9 %) Doses : 0, 250, 500, 3000 and 1000/4000 ppm Exposure 90 days Vehicle : ethanol	A lower bw was seen at the 2 highest dose levels. Organ weight examination showed a lower brain weight at 3000 ppm in both sexes and also in males at 1000/4000 ppm. In conjunction, degeneration/necrosis on the cerebellum and degeneration of some nerve fibers were observed. At the 2 highest dose levels, a slight increased number of corpora lutea was noted. The FOB revealed some effects such as tremors, gait incoordination, … at the 2 highest dose levels. NOAEL : 500 ppm	Wahle B.S. and Sheets L.P., 2004 (cited in JMPR, 2008)
Chronic toxicity study in rats (Crl:Wi(han)) (20/sex/dose) Oral (feed) Following OECD TG 452 GLP	1,2,4-triazole (purity ≥98.5 %) Doses : 0, 125, 375, 1000 and 2000 ppm Exposure : 12 months Vehicle : ethanol	A slight decrease of bw and bwg was seen at the 2 highest doses. The histopathological examination revealed a significant higher incidence of Purkinje cells loss at 2000 ppm. No effects were observed during oestrous cycle and sperm analysis. NOAEL : 375 ppm	Wahle B.S., 2010

10.10.1.2. Human information.

No information available

10.10.1.3. Other relevant information

No information available

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

In a two-generation reproductive toxicity study performed following the OECD guideline 416 (Young A.D. and Sheets L.P., 2005), groups of 30 male and 30 female rats were given diets containing 1,2,4-triazole at a concentration of 0, 250, 500 or 3000 ppm (See table 15 for the dosing in mg/kg bw/d during the different exposure periods).

For females, the exposure period began 10 weeks before mating, and continued through mating, gestation, and lactation. During lactation, dietary levels were reduced to maintain a more constant dosage (mg/kg/day) throughout the study. Following the weaning of their litters on lactation D21, each dam was sacrificed. Due to the low fertility at the highest dose (3000 ppm), this dose level was stopped after gestation in P-gen females an therefore no animal was exposed to this dose level in the F1-generation. Males were only exposed during a premating period of 10 weeks.

Table 15 : dose level by group in mg/kg bw/d (Young A.D. and Sheets L.P., 2005)

	Phase of study	250 ppm in mg/kg bw/d	500 ppm in mg/kg bw/d	3000 ppm in mg/kg bw/d
♂	Premating (P-gen)	15.4	30.9	188.6
	Premating (F1-gen)	16	32	NA
♀	Premating (P-gen)	17.5	36.2	217.9
	Gestation (P-gen)	18.6	38.6	231.7[a]
	Lactation (P-gen)	19.3	38.7	NA
	Premating (F1-gen)	18.9	37.5	NA
	Gestation (F1-gen)	17.4	34.4	NA
	Lactation (F1-gen)	20.3	35.8	NA

[a] *: based on only 2 pregnant females*

No treatment-related effects were observed concerning deaths or clinical signs at any dietary dose level. Bw of males and females was significantly modified during different exposure periods (see table 16).

Table 16 : body weight data in grams for P and F1 animals (Young A.D. and Sheets L.P., 2005)

	Phase of study	0 ppm	250 ppm	500 ppm	3000 ppm
	P D0	294.0	291.6	298.4	299.7
♂	P terminal bw	473.1	460.7	456.1	419.4*
	P BWG	179.1	169.1	157.7	119.7
	F1 D0	266.2	254.3	250.6*	/
	F1 terminal bw	464.5	440.8*	426.6*	/
	F1 BWG	198.3	186.5	176.0	/
	P D0	206.1	206.8	209.2	209.5
♀	P premating-mating (D70)	244.1	244.9	239.5	233.4*
	P gestation (D20)	345.3	340.9	340.0	284.7**[a]
	P lactation (D21)	284.2	287.4	287.4	/
	P terminal bw	277.2	283.1	280.9	245.1*[a]
	P BWG	71.1	76.3	71.7	35.6[a]
	F1 D0	172.3	166.7	169.1	/
	F1 premating-mating (D70)	236.2	227.5	230.8	/
	F1 gestation (D20)	323.8	313.3	311.8	/
	F1 lactation (D21)	281.4	267.8*	271.2	/
	F1 terminal bw	277.2	262.9*	265.7	/
	F1 BWG	104.9	96.2	96.6	/

** : p≤0.05* *** : p≤0.0* *1*[a] : based only on 2 dams

Males and females of the F0-generation at the highest dose had a significantly lower terminal bw (473.1/277.2, 460.7/283.1, 456.1/280.9 and 419.4*/245.1* g respectively at 0, 250, 500 and 3000 ppm in males/females) and lower absolute brain weight (2.092/1.955, 2.075/1.941, 2.044/1.951 and 2.006*/1.853* g at 0, 250, 500 and 3000 ppm in males/females, respectively) compared with the control group. Several other organs also showed modifications at this highest dose such as ovaries (0.058/0.058, 0.059/0.057, 0.055/0.054 and 0.067*/0.071* g (left/right ovaries) respectively at 0, 250, 500 and 3000 ppm), thyroid, and liver. In addition to the brain weight changes, minimal to marked degeneration/necrosis was observed in 30 out of 30 males and in 28 out of 30 females. Moreover, in the ovaries, changes in number of total corpora lutea was observed (24.9, 23.0, 15.6 and 41.3 at 0, 250, 500 and 3000 ppm, respectively). Finally, the histopathological examination of the uterus revealed a higher incidence of dilatation (14* females at 3000 ppm vs 4 females in control group).

During this study, male and female fertility parameters were analyzed and revealed some modifications in P-generation (see table 17 and 18). Only two litters containing one female pup each were produced by the F0-generation at 3000 ppm.

Table 17 : Sperm parameters in the P-generation (Young A.D. and Sheets L.P., 2005)

	Sperm motility		Total sperm count		Sperm morphology		
	% motile	% progressive	Epididymis	Testis	% normal	% abnormal	% detached
0 ppm	76.2	55.9	58.2	72	98.7	0.8	0.5
250 ppm	78.9	56.5	57	63.1*	98.1	1	0.8
500 ppm	78.9	56.4	65.7	64.4	97.0*	1.4*	1.6*
3000 ppm	78.9	57.3	43.2*	61.2*	95.7*	1.5*	2.8*

* : $p \leq 0.05$

Table 18 : Reproductive data from the P-generation (Young A.D. and Sheets L.P., 2005)

	Nb of estrous cycle	Estrous cycle length (d)	Mating index (%)	Fertility index (%)	Nb of implantations	Duration of gestation	Mean nb of live pups	Sex ratio (% males)	Viability index
0 ppm	3.6	4.2	100.0	76.7	265	22.3	233	54.1	96.2
250 ppm	3.8	4.2	100.0	83.3	310	22.0	279	55.4	97.1
500 ppm	3.4	4.4	96.7	86.2	279	22.2	260	50.7	99.6
3000 ppm	3.6	4.2	93.3	7.1**	3	23.5	2	/	100.0

* : $p \leq 0.05$, ** : $p \leq 0.01$

At the highest dose level, the number of live pups was severely decreased. At this dose level, mean F1-pups bw was significantly decreased at D7 but this mean value was calculated using the data of the only 2 live pups (16.5, 15.8, 15.7 and 9.1** g respectively at 0, 250, 500 and 3000 ppm).

Due to low fertility at 3000 ppm, further testing with this dose in the next generation was not performed.

The trend to lower terminal bw observed at the P-generation was also observed during the F1-generation (464.5/277.2, 440.8*/262.9* and 426.6*/265.7 respectively at 0, 250 and 500 ppm in males/females). No significant changes were observed during organ weight examination.

During this F1-generation, no significant changes were shown in male and female reproductive parameters (see table 19 and 20). However, a slight decreasing trend in fertility index and number of implantations was observed.

Table 19 : Sperm parameters in the F1-generation (Young A.D. and Sheets L.P., 2005)

	Sperm motility	Total sperm count	Sperm morphology

	% motile	% progressive	Epididymis	Testis	% normal	% abnormal	% detached
0 ppm	87.1	63.9	49.2	69.2	98.1	1.1	0.8
250 ppm	87.8	65.7	NE	NE	NE	NE	NE
500 ppm	89.5	67.6	48.6	68.3	97.9	1.4	0.7

* : $p \leq 0.05$

Table 20 : Reproductive data in the F1-generation (Young A.D. and Sheets L.P., 2005)

	Nb of estrous cycle	Estrous cycle length (d)	Mating index (%)	Fertility index (%)	Nb of implantations	Duration of gestation	Mean nb of live pups	Sex ratio (% males)	Viability index
0 ppm	3.7	4.1	100.0	93.3	304	22.1	280	48.7	99.7
250 ppm	3.7	4.1	100.0	86.7	300	21.9	287	47.3	98.8
500 ppm	3.8	4.1	96.7	86.2	273	21.8	260	40.6	95.6

According to the results, the NOAEL for the parental toxicity was set at 500 ppm based on lower bw and degenerative findings observed in the cerebellum at the highest dose level. The NOAEL for fertility could not be determined based on the reduction in testicular sperm counts noted at 250 ppm. Moreover, the NOAEL for developmental toxicity is 500 ppm which was the highest dose allowing assessment of the developmental effects as the 3000 ppm dose level was not further tested due to the low number of pups obtained.

In a 28-day repeated dose toxicity study (Wahle B.S., 2004a), groups of 15 male and 15 female mice received diets containing 1,2,4-triazole at a concentration of 0, 50, 250, 500 or 2000 ppm (corresponding to 0, 9, 47, 90 and 356 mg/kg bw/d in males and 0, 12, 60, 120 and 479 mg/kg bw/d in females).

No treatment-related effects were observed on survival, clinical signs, bw, food consumption, clinical chemistry parameters or on organ weights.

Nevertheless, the histopathological evaluation revealed some modifications in testes and in epididymis as reported in the table 21.

Table 21 : Incidence of testicular and epididymal lesions in mice (Wahle B.S., 2004a)

Observed effects		Dietary concentration in ppm				
		0	50	250	500	2000
Epididymis	Incidence of aspermia	0/15	0/15	0/15	1/15	0/15
	Incidence of exfoliated germ cells/debris	0/15	1/15 (1)	1/15 (3)	0/15	3/15 (2)
Testis	Testicular degeneration	3/15	ND	ND	ND	5/15
	Incidence of apoptotic-like bodies	2/15 (1)	4/15 (1)	1/15 (1)	3/15 (1)	5/15 (1)
	Incidence of spermatid degeneration/depletion/asynchrony	1/15 (1)	1/15 (1)	1/15 (1)	0/15	5/15 (1.4)
	Incidence of focal tubular atrophy	1/15 (1)	2/15 (1)	1/15 (2)	2/15 (2)	4/15 (1.8)

() : average severity score (1 minimal to 5 severe)

Based on the results, the NOAEL was 500 ppm in males (equivalent to 90 mg/kg bw/d) and 2000 ppm in females (equivalent to 479 mg/kg bw/d).

In a 30-day repeated dose toxicity study (anonymous cited in US EPA memorandum, 2006), rats were orally exposed to 1,2,4-triazole at a concentration of 0, 8, 57 or 400 mg/kg bw/d.

A few effects were revealed during this study such as a lower bw and some clinical signs at the highest dose level. Slight hematological changes were noted at 57 mg/kg bw/d and a lower adrenal weight was seen at 8 mg/kg bw/d. No further data were reported.

Based on the poorly available data, the NOAEL was < 8 mg/kg bw/d.

In a 90-day repeated dose toxicity study (Bomhard E. et al., 1979), groups of 15 male and 15 female rats were exposed to 1,2,4-triazole at a concentration of 0, 100, 500 or 2500 ppm (equivalent to 0, 7.79, 37.85 and 212.30 mg/kg bw/d in males and to 0, 10.23, 54.20 and 266.69 mg/kg bw/d in females).

The mortality and the food consumption were regarded but no modifications were observed. In the highest dose group, 2 males and 2 females exhibited slight temporary convulsions. Bw and bwg parameters in the low and mid dose level were in the same range than the control group whereas, in the highest dose group, there was a significantly lower bw in males for the entire study period and in females at the majority of the observation dates. The mean initial bw was of 82, 82, 82 and 82 g in males and of 78, 78, 78, and 78 g in females, both at 0, 100, 500 and 2500 ppm, respectively. The terminal bw was 335, 342, 344 and 306** g in males and 195, 195, 187 and 184* g in females respectively at 0, 100, 500 and 2500 ppm.

The absolute testis weight was decreased at the highest dose (3418, 3308, 3247 and 3215* mg respectively at 0, 100, 500 and 2500 ppm). However, no histopathological lesions were observed in this organ.

According to the results, the NOAEL was 500 ppm (corresponding to 37.85 mg/kg bw/d in males and to 54.20 mg/kg bw/d in females).

In a 90-day repeated dose toxicity study (Wahle B.S., 2004b), groups of 20 male and 20 female mice were exposed orally (via diet) to 1,2,4-triazole at a concentration of 0, 500, 1000, 3000 or 6000 ppm (corresponding to 0, 80, 161, 487 and 988 mg/kg bw/d in males and to 0, 105, 215, 663 and 1346 mg/kg bw/d in females). Moreover, additional groups of 15 males and 15 females were exposed for 28 days and then killed for hepatic enzymes analysis.

No treatment-related effects were observed on mortality. However, an increased incidence of tremors was observed in both sexes at the highest dose level (0/0, 0/0, 0/0, 1/2 and 11/2 respectively at 0, 500, 1000, 3000 and 6000 ppm in males/females). And during this clinical observation at this dose, a higher incidence of yellow staining and rough coat were also noted in males. Furthermore, the analysis of hepatic enzymes profiles showed an increased activity of ECOD, EROD, ALD and GLU-T in both sexes at 6000 ppm.

Bw were decreased through the study in both sexes as reported in table 22.

Table 22 : Bw at D84 (Wahle B.S., 2004b)

		0 ppm	500 ppm	1000 ppm	3000 ppm	6000 ppm
Bw at D84 (in g)	♂	37.3	37.0	36.4	34.9*	31.3*
	♀	29.1	28.4	28.4	28.7	26.6*
Total bwg (in g)	♂	3.1	3.6	1.7	1.1*	-3.1*
	♀	3.5	3.1	3.0	2.7	0.9*

* $p \leq 0,05$

Concerning the organ weight and the histopathological examination, brain and testes exhibited modifications. The absolute brain weight was significantly decreased in both sexes at 6000 ppm and also in males at 3000 ppm. In addition, an increased incidence of Purkinje cell loss was observed in both sexes at the highest dose. Furthermore, absolute testis weight was significantly decreased at 6000 ppm. In conjunction with this change, histopathological modifications were observed including increased incidence of apoptotic-like bodies, of spermatid degeneration/depletion/asynchrony and of tubular atrophy. These changes were generally dose-dependent in incidence and severity. Moreover, the epididymal histopathological examination revealed also a higher incidence of exfoliated germ cells and debris in the lumen of the duct at 6000 ppm.

Table 23 : Organ weight and histopathological findings (Wahle B.S., 2004b)

			0 ppm	500 ppm	1000 ppm	3000 ppm	6000 ppm
Term. Bw (in g)		♂	36.9	35.8	34.9*	33.9*	30.5*
		♀	28.1	27.9	28.0	27.9	26.0*
Brain	Abs. weight (in g)	♂	0.488	0.491	0.476	0.465*	0.445*
		♀	0.485	0.489	0.483	0.475	0.451*
	Rel. weight (in %)	♂	1.328	1.378	1.365	1.376	1.462*
		♀	1.737	1.756	1.731	1.717	1.734
	Incidence of Purkinje cell loss	♂	0/20	0/20	0/20	0/20	15*/20 (1.7)
		♀	0/20	0/20	0/20	0/20	10*/20 (1.3)
Testis	Abs. weight (in g)		0.253	0.247	0.233	0.233	0.219*
	Rel. weight (in %)		0.688	0.692	0.669	0.687	0.719
	Incidence of apoptotic-like bodies		4/20 (1.0)	4/20 (1.3)	7/20 (1.1)	11*/20 (1.3)	12*/20 (1.2)
	Incidence of spermatid degeneration/depletion/asynchrony		1/20 (1.0)	0/20	0/20	5/20 (1.4)	15*/20 (2.0)
	Incidence of tubular atrophy		0/20	0/20	2/20 (1.5)	3/20 (1.0)	10*/20 (1.8)
Epididymis	Incidence of exfoliated germ cells/debris		0/20	0/20	0/20	0/20	10*/20 (2.5)

() : average severity score (1 minimal to 5 severe); * $p \leq 0.05$

Based on the results of the study, the NOAEL was 1000 ppm in males (corresponding to 161 mg/kg bw/d) and 3000 ppm in females (corresponding to 663 mg/kg bw/d).

A combined 90-day repeated dose toxicity study and neurotoxicity study (Wahle B.S. and Sheets L.P., 2004) was performed following the OECD guidelines 408 and 424. Groups of 20 male and 20 female rats were exposed to 1,2,4-triazole at a concentration of 0, 250, 500, 3000 or 1000/4000 ppm (corresponding to an average daily intake over about 14 weeks at the precited nominal dietary concentrations of 0, 16, 33, 183 and 210 mg/kg bw/d in males and 0, 19, 41, 234 and 275 mg/kg bw/d in females). The dose of 1000 ppm has been modified after 4 weeks to 4000 ppm. Concerning the highest dose level, the daily intake value shows

the average of approximately 4 weeks of exposure at 1000 ppm and approximately 10 weeks of exposure at 4000 ppm. The mean daily intake for 1000/4000 ppm animals through week 4 was 85 + 3 and 95 + 3, for males and females respectively while the mean daily intake values until the end of the study was 248 + 16 and 329 + 21, for males and females respectively.

No treatment-related effects were observed on mortality, food consumption, hematology and urine analysis parameters.

A functional observational battery (FOB) examination revealed changes at the two highest dose levels such as ungroomed appearance, red nasal stain, urine stain muscle fasciculations, gait incoordination, decreased activity in open field in males and tremor and decreased rearing in both sexes at 3000 ppm. Red nasal stain, decreased activity in the open field and increased splayfoot were seen in males, urine stain in females and ungroomed appearance, muscle fasciculations, tremor, gait incoordination, decreased rearing and uncoordinated righting in both sexes at 1000/4000 ppm dose level.

Bw was unaffected up to 500 ppm dose level however at the two highest doses a decrease was observed in both sexes (table 24).

Evaluation of clinical chemistry parameters revealed a slight decrease of serum triglyceride concentration in 3000 and 1000/4000 ppm dose levels and a slight increased activity of the hepatic enzymes such as N-demythylase, O-demythylase, ECOD, EROD, ALD, EH, GS-T and GLU-T. Moreover, a significant decrease in TSH concentration was seen in males at 500, 3000 and 1000/4000 ppm (4.68*, 4.58* and 4.14* ng/ml vs 6.35 ng/ml in control group). No organ weight change or histopathological modification confirmed these clinical chemistry changes. The only organ weight which was significantly disturbed was the absolute brain weight (in males : 1.94* g and 1.92* g respectively at 3000 and 1000/4000 ppm vs 2.05 g in control group, in females : 1.78* g and 1.81 g respectively at 3000 and 1000/4000 ppm vs 1.91 g in control group). In conjunction of these brain weight changes, the necropsy revealed some histopathological changes such as an increased incidence of degeneration/necrosis of the brain level 7 (9 out of 10 males at 1000/4000 ppm and 10 out of 10 at 3000 ppm vs 0 out of 10 in control group and 10 out of 10 females at the 2 highest dose level vs 0 out of 10 in control group), some increased incidence of degeneration of nerves (sciatic nerve left and right, tibial nerve left and right, sural nerve left and right).

A lower uterus weight was also observed but it was not statistically significant (0.611, 0.568, 0.602, 0.521 and 0.491 respectively at 0, 250, 500, 1000/4000 and 3000 ppm).

A slight increase in number of corpora lutea was observed in females at 3000 pmm and 1000/4000 ppm (see table 24).

Table 24 : Body weight data and corpora lutea information (Wahle B.S. and Sheets L.P., 2004)

		0 ppm	250 ppm	500 ppm	3000 ppm	1000/4000 ppm
Bw (D0) (in g)	♂	265.6	267.4	267.0	267.1	266.1
	♀	181.2	181.4	180.7	179.9	182.7
Bw (D91) (in g)	♂	437.9	439.7	443.0	407.9*	401.9*
	♀	245.1	246.9	244.4	231.7*	233.0
Bwg (D0 - D91) (in g)	♂	172.3	172.2	176.0	140.8*	135.9*
	♀	63.9	65.5	63.7	51.8*	50.3*
Total corpora lutea		33	NE	33	41	40
Recent cycle corpora lutea		16	NE	17	21	19

NE : not evaluated; * $p \leq 0.05$

According to the results, the NOAEL for this combined study was set at 500 ppm.

In a chronic repeated dose toxicity study performed following the OECD guideline 452 (Wahle B.S., 2010), groups of 20 male and 20 female rats were exposed to 1,2,4-triazole during 12 months at a concentration of 0, 125, 375, 1000 and 2000 ppm (corresponding to 0, 6.9, 21, 58 and 113 mg/kg bw/d in males and 0, 8.3, 26, 71, 136 mg/kg bw/d in females). Furthermore, additional groups of 10 animals/sex/group were exposed to analyze neurotoxicity parameters.

No treatment-related effects were observed in the mortality, clinical signs, food consumption, hematology, clinical chemistry, organ weight, gross pathology, estrous cycle staging and sperm analysis examinations.

A lower bw and bwg were observed in both sexes at the 2 highest dose groups (BWG (D0 - D343) : 293/116 g at 1000 ppm, 294/115 g at 2000 ppm vs 318/144 g in control group in males/females, respectively).

Neurological assessment, comprising a FOB and a motor activity examination, was performed and revealed no treatment-related effect at any dietary dose level in both sexes.

The histopathology examination showed changes in the brain at the highest dose level. The lesion was characterized as an increased incidence of Purkinje cells loss within the vermis.

Table 25 : Incidence of Purkinje cell loss (Wahle B.S., 2010)

	0 ppm		2000 ppm	
	Toxicology group	Neurotoxicology group	Toxicology group	Neurotoxicology group
Males	0/20	0/10	10/10	6/10
Females	0/20	0/10	14/20	7/10

According to the results, the NOAEL was established to be 375 ppm for both sexes based on the lower observed bw and bwg.

10.10.3 Comparison with the CLP criteria

As there are no epidemiological studies available, Cat. 1A is not warranted.

According to the CLP Regulation (EC No 1272/2008) the classification of a substance in category 1B for reproductive toxicants *"is largely based on data from animals studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in category 2 may be more appropriate"*.

In the 2-generation reproductive toxicity study performed in rats (Young A.D. and Sheets L.P., 2005), almost complete infertility was observed at the top dose (fertility index: 76.7, 83.3, 86.2 and 7.1 % at 0, 250, 500 and 3000 ppm, respectively) in the P generation only, considering the highest dose was not tested in F1. Therefore, clear evidence of an adverse effect on fertility at the top dose was shown. The adverse effect occurred together with other toxic effects. At the highest dose, mild to moderate brain cerebellar degeneration/necrosis was observed in both sexes in the parental generation. Nevertheless, the cerebellum is not involved in the reproductive axis (hypothalamic-pituitary-gonadal axis). Furthermore, maternal body weight during gestation period was statistically significantly reduced at the highest dose however, this modification could be explained by the low number of pregnant females (since 28 out of 30 dams were not pregnant). The adverse effects on fertility are not considered to be secondary non-specific consequences of systemic toxicity since systemic toxicity appeared to be minimal. Further more, adverse effects on fertility are supported by other effects observed in this study : increased incidence of uterus dilatation, reduction in epididymal sperm counts and reduction of normal sperm morphology percentage can also explain the fertility adverse effects.

Furthermore, a few studies revealed histopathological modifications in testis. In a subacute toxicity study (Wahle B.S., 2004a), an increased incidence of spermatid degeneration/depletion/asynchrony was observed without any other signs of toxicity (no effects on survival, clinical signs, bw or organ weigth). This effect was confirmed by a subchronic toxicity study (Wahle B.S., 2004b) in which a statistically significant higher incidence of spermatid degeneration/depletion/asynchrony was also noted. In this last study, an increased incidence of tremors, yellow staining and rough coat were observed in males at the highest dose, the bw was also modified however these effects are not considered severe enough to explain the important modifications observed in testis and epididymis. In a combined 90-day repeated dose toxicity study and neurotoxicity study (Wahle B.S. and Sheets L.P., 2004), a lower uterus weight and a slight increased number of corpora lutea were observed at the 2 highest dose levels (3000 ppm and 1000/4000 ppm). Simultaneously, a bw change was noted which was significant only at 3000 ppm).

According to the CLP Guidance a classification as Repro 1B for adverse effects on sexual function and fertility is warranted based on the above mentioned severe effects observed in the available studies, which cannot be related to a general toxicity.

The CLP regulation (EC No 1272/2008) also states that "*Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification*". Cat.2 is not recommended considering the clear impact of 1,2,4-triazole on the fertility, as showed above. It is considered that the effects observed are sufficiently convincing to propose a cat. 1B.

10.10.4 Adverse effects on development

10.10.4.1 Non-human information

Table 26 : Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Embryotoxicity study in rats (Bor : Wisw (SPF Cpb)) (25 females/group) Oral EPA OPPTS 83-3 guidance GLP	1,2,4-triazole (purity 94,0 %) Doses : 0, 100 and 200 mg/kg bw/d Exposure : GD 6-15 Vehicle : cremophor-EL emulsion 0.5 %	<u>Dams :</u> No mortality and no clinical signs observed. At the highest dose, bw was decreased at GD 20 and the bwg was significantly modified. No significant changes were seen in the number of dams fertilised or in the number of implantation sites per dam, but a significant increase in post-implantation loss (0.5, 0.3 and 6.3** at 0, 100 and 200 mg/kg bw/d, respectively) was observed only in the highest dose level leading to a high rate of resorptions of 53 %. The mean number of corpora lutea per dams was significantly increased (14.2* at 200 mg/kg bw/d vs 13.6 in control group). <u>Foetus :</u> The mean number of foetus per dams was significantly decreased at the highest dose	Renhof M., 1988a

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		(5.5** at 200 mg/kg bw/d vs 12.0 in control group). The mean foetus weight was significantly reduced at the 2 tested doses (3.55, 3.06** and 2.35** g at 0, 100 and 200 mg/kg bw/d, respectively). The mean placental weight was significantly decreased (0.59, 0.52** and 0.49** g at 0, 100 and 200 mg/kg bw/d, respectively). The number of foetus per litter with malformations was increased at the highest dose (0.80* vs 0.29 in control group) NOAEL (maternal toxicity) : 100 mg/kg bw/d NOAEL (developmental toxicity) : < 100 mg/kg bw/d	
Embryotoxicity study in rats (Bor : Wisw (SPF Cpb)) (25 females/group) Oral EPA OPPTS 83-3 guidance GLP	1,2,4-triazole (purity 95.3 %) Doses : 0, 10, 30 and 100 mg/kg bw/d Exposure : GD 6-15 Vehicle : cremophor-EL emulsion 0.5 %	<u>Dams :</u> No mortality observed Bwg during exposure period was significantly reduced at the highest dose (28.2, 25.4, 26.8 and 21.8*g at 0, 10, 30 and 100 mg/kg bw/d, respectively). No modification in the number of implantations per dams. <u>Foetus :</u> A significant increased incidence of runts was observed at the highest dose (0.33, 0.23, 0.53 and 2.21** at 0, 10, 30 and 100 mg/kg bw/d, respectively) A significant lower foetal weight was observed at the highest dose (3.25 vs 3.58 g in control group). No dose-related increased incidence of malformation. NOAEL (maternal toxicity) : 30 mg/kg bw/d NOAEL (developmental toxicity) : 30 mg/kg bw/d	Renhof M., 1988b
Developmental study in rats (Wistar) (10 females/dose) Oral Non-guideline, non-GLP	1,2,4-triazole (purity : no information available) Doses : 0, 25 and 100 mg/kg bw/d Exposure : GD 7 through 17 Vehicle : no information available	<u>Maternal observation :</u> Bw not affected <u>Offspring observation :</u> No effects were observed on litter weight (PND 1 and 5) and on number of live and dead pups (PND 1 and 5) NOAEL(maternal toxicity) : 100 mg/kg bw/d NOAEL (developmental toxicity) : 100 mg/kg	Wickramaratne, 1987 (cited in JMPR, 2008)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		bw/d	
Prenatal developmental toxicity study in rabbits (NZW) (25females/dose) Oral (gavage) Following OECD TG 414 GLP	1,2,4-triazole (purity 99.9 %) Doses : 0, 5, 15, 30 and 45 mg/kg bw/d Exposure : GD 6-28 Vehicle : aqueous 0.5 % carboxymethylcellulose	Dams : Mortality : at the highest dose, 5 females were sacrified due to their moribund condition. The bwg over the entire gestation was significantly reduced at the highest dose (0.37** g vs 0.65 g in control group). However, the maternal bw at GD 29 was not modified significantly. A significant lower gravid uterine weight was observed at the highest dose (0.46** kg vs 0.56 kg in control group). No modification in the number of coropora lutea, the number of implantations, the litter size, the incidence of early and late resorptions. Foetus : The live foetal bw was significantly reduced at the highest dose (39.46** g vs 44.35 g in control group). Moreover, a higher incidence of alterations of the urogenital system was observed at the highest dose. NOAEL (maternal toxicity) : 30 mg/kg bw/d NOAEL (developmental toxicity) : 30 mg/kg bw/d	Hoberman, 2004 (cited in JMPR, 2008)
2-generation reproductive toxicity study in rats (Wistar Hannover) (30/sex/dose) Oral (diet) Following OECD TG 416 GLP	1,2,4-triazole (purity 99,9 %) Doses : 0, 250, 500 and 3000 ppm Exposure : through 10 weeks premating period to lactation D21 Vehicle : ethanol	No treatment-related effects were observed concerning deaths or clinical signs at any dietary dose level. Bw of males and females was statistically modified during different exposure periods (see table 37). P0 : Brain weight was significantly reduced at 3000 ppm in both sexes in P0. In conjunction with brain weight, degeneration/necrosis was observed in the cerebellum. Absolute and relative ovarian weights was significantly increased at 3000 ppm in P0 females. Furthermore, changes in the number of corpora lutea was noted. Modification of sperm parameters were observed. In females, reproductive data were also modified. No treatment-related effects were observed concerning the sex ratio, the viability index, the mean litter or pup weights and the	Young A.D. and Sheets L.P., 2005

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		micropathology evaluation of the pups. NOAEL (parental toxicity) : 500 ppm NOAEL (fertility) : < 250 ppm based on the sperm parameters NOAEL (developmental toxicity) : 500 ppm	

10.4.2. Human information

No information available

10.4.2.3 Other relevant information

No information available

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

An embryotoxicity study has been performed in rats (Renhof, 1988a, cited in JMPR, 2008) with 1,2,4-triazole of 94% purity. Impurities were not specified but the study was performed with the same batch as the Renhof, 1988b –study for which 2 impurities were identified. Those impurities have a harmonized classification and labeling : Repr.1B, H360D *** and Repr. 2, H361d***resp. and can contribute to the classification if their concentration is ≥ 0.3% (Repr. 1B) or ≥3% (Repr.2). Analytical analysis of the batch used in the Renhof, 1988b , confirmed that >0.3% of the impurity with HCL Repr.1B was available, but <3% of the impurity with HCL Repr.2.

25 females per group were orally exposed to 1,2,4-triazole at doses of 0, 100 or 200 mg/kg bw/d from gestational day 6 to 15.

All animals survived during the study and no maternal treatment-related clinical signs or food consumption changes were observed. The maternal bw evaluation revealed a slight tendency to decrease which was confirmed by the bwg data (see table 29).

Table 29 : Bw and bwg data (in g) (Renhof, 1988a, cited in JMPR, 2008)

	Bw at GD 0	bw at GD 6	bw at GD 15	bw at GD 20	bwg during exposure period	bwg during entire pregnancy	Mean gravid uterus weight	Adjusted maternal body weight gain
0 mg/kg bw/d	204.6	221.5	250.9	301.4	29.3	96.8	66	30.8
100 mg/kg bw/d	203.8	222.5	249.8	295.7	27.4	91.9	57.74	34.16
200 mg/kg bw/d	203.2	220.3	241.8	263.6	21.5*	60.4**	27.16	33.24

* p < 0.05 **p<0.01

Concerning the pregnancy parameters, there were no treatment-related effects.

The fetal evaluation exhibited a lower bw and a lower placental weight at 100 and 200 mg/kg bw/d. Furthermore, the incidence of runts was significantly higher at 100 and 200 mg/kg bw/d. In addition of these modifications, the number of surviving fetuses per dam was reduced and the incidence of fetuses with malformations (undescended testicle, cleft palate and hydronephrosis) was increased at the highest dose level. Moreover, the number of resorptions per litter was increased at the highest dose level (53.2 % vs 3.9 % in controls). (See table 30 and table 31)

Table 30 : Intrauterine development parameters (Renhof, 1988a, cited in JMPR, 2008)

	0 mg/kg bw/d	100 mg/kg bw/d	200 mg/kg bw/d
Nb of corpora lutea per dam	13.6	13.9	14.2*
Nb of implantation per dam	12.5	12.2	11.8
Nb of runts per litter	0.24	2.84*	4.96**
Number of fetuses per dam	12.0	11.9	5.5**
Number of male/female fetuses per dam	5.9/6.1	6.0/5.9	3.1**/2.4**
Nb of post-implantation loss per dam	0.5	0.3	6.3**
Mean fetuses weight (in g)	3.55	3.06**	2.35**
Mean placental weight (in g)	0.59	0.52*	0.49**
Fetuses per litter with minor skeletal deviations	2.67	4.32*	2.24
Fetuses per litter with malformation	0.29	0.63	0.80*

* p < 0.05 **p<0.01

Table 31 : Observed malformations (Renhof, 1988a, cited in JMPR, 2008)

	0 mg/kg bw/d	100 mg/kg bw/d	200 mg/kg bw/d
Total incidence of undescended testicle	2/253 (0.8 %)	11/226 (4.9 %)	6/138 (4.3 %)
Incidence per litter of undescended testicle	2/21 (9.5 %)	7/19 (36.8 %)	5/25 (20 %)
Total incidence of hydronephrosis	1/253 (0.4 %)	1/226 (0.4 %)	7/138 (5.1 %)
Incidence per litter of hydronephrosis	1/21 (4.8 %)	1/19 (5.3 %)	6/25 (24 %)
Total incidence of cleft palate	0/253	0/226	4/138 (2.9 %)
Incidence per litter of cleft palate	0/21	0/19	3/25 (12 %)

Based on the results, the NOAEL for maternal toxicity was 100 mg/kg bw/d however the NOAEL for developmental toxicity was inferior to the low dose group level which was 100 mg/kg bw/d.

Contribution of the impurity (HCL : Repr.1B and conc. >0.3%) to the classification :

In the key developmental toxicity study (reliability 1) no statistical significant differences were observed in the incidences of fetal morphological anomalies, the overall incidences were approximately 1.3 (control), 2.2, 0.6, and 1.3% for the respective groups.

A NOAEL of 50 mg/kg bw/d was established, based on decreases in fetal body weight.

The average male and female fetal weight was statistically significantly reduced at 100 and 200 mg/kg bw/day. The number of fetuses per litter and fetal viability were not affected. The sex distribution was not changed. The incidence of external, skeletal or visceral malformations and variations was not increased at any dose. In this study, the rat conceptus was more sensitive than the adult to the adverse effects of formamide administered orally throughout the embryo/fetal period of gestation.

The developmental NOAEL was 50 mg/kg bw/d was established, based on decreases in fetal body weight. Teratogenicity was not seen, the NOAEL was therefore 200 mg/kg bw/day (NTP, 1998).

No cleft palate was observed in the study performed with the Repr. 1B impurity. This demonstrates that this impurity exerts another mode of action than in the Renhof study(1988a). It can be concluded that the severe malformation (cleft palate) was due to 1,2,4-triazole and not to the impurity.

Furthermore the increased incidence of cleft palates in rat has also been observed in response to exposure to other triazoles like propiconazole, cyproconazole and epoxiconazole.

Therefore we can conclude that the Renhof (1988a) study is adequate and reliable for the classification of 1,2,4-triazole for adverse effects on development.

A second embryotoxicity study has been performed in rats (Renhof, 1988b, cited in JMPR, 2008) with 1,2,4 triazole (purity 95,3%). Impurities were not specified.

25 females by group were given 1,2,4-triazole at doses of 0, 10, 30 or 100 mg/kg bw/d from gestational day 6 to 15.

Concerning maternal evaluation, all animals survived during the study and no treatment-related clinical signs or food consumption changes were observed. However, the bwg was significantly lower at 100 mg/kg bw/d during the exposure period than in the control group (21.8* g vs 28.2 g).

Considering the pregnancy parameters, there were no treatment-related effects.

Concerning intrauterine development, up to 30 mg/kg bw/d dose level the examined parameters were unaffected. Nevertheless, at the highest dose level, a few parameters were disturbed such as fetal weight which was significantly decreased and simultaneous greater incidence of runts. Moreover, at this dose level, a slight increase in the number of malformations was observed. However, it affected only one fetus for each type of malformation and therefore was considered not treatment-related. (See table 32 and table 33)

Table 32 : Effects on intrauterine development (Renhof, 1988b, cited in JMPR, 2008)

	0 mg/kg bw/d	10 mg/kg bw/d	30 mg/kg bw/d	100 mg/kg bw/d
Nb of implantation per dam	11.6	10.5	11.4	10.6
Nb of runts per litter	0.33	0.23	0.53	2.21*
Number of fetuses per dam	11.0	10.1	10.6	9.5
Number of male/female fetuses per dam	6.5/4.5	5.1*/5.0	6.0/4.6	5.0*/4.5
Mean fetuses weight (in g)	3.58	3.59	3.53	3.25**
Mean placental weight (in g)	0.56	0.56	0.57	0.56
Fetuses per litter with minor skeletal deviations	2.00	2.41	2.84	2.42
Fetuses per litter with malformation	0.05	0.05	0.05	0.17

* $p < 0.05$ **$p<0.01$

Table 33 : Incidence of malformation (Renhof, 1988b, cited in JMPR, 2008)

	0 mg/kg bw/d	10 mg/kg bw/d	30 mg/kg bw/d	100 mg/kg bw/d
Total no. examined foetuses	231	222	202	228
Microphtalmia, bilateral	1	0	0	0
Microphtalmia, right side	0	1	0	1

Microphtalmia, left side	0	0	0	1
False posture of right hind leg	0	0	1	0
Anophtalmia	0	0	0	1
Dysplasia and asymmetry of body of vertebrae	0	0	0	1

According to the results, the NOAEL for maternal and developmental toxicity was set at 30 mg/kg bw/d.

In a non-guideline developmental toxicity study (Wickramaratne, 1987, cited in JMPR, 2008), non-GLP, 10 females rats were exposed to 1,2,4-triazole (purity and vehicle not reported) at doses of 0, 25 or 100 mg/kg bw/d from day 7 to 17 of gestation.

Examined maternal parameters were restricted to bw and no change was observed.

Offspring observation was also restricted to only few parameters such as litter weight of live pups on PND 1 and 5 and the number of live and dead pups on these days. During these examinations, no effects were noted.

Based on the available results, the NOAEL for maternal and developmental toxicity was established to be 100 mg/kg bw/d.

In a prenatal developmental toxicity study (Hoberman, 2004, cited in JMPR, 2008), following OECD guideline 414, 25 pregnant female rabbits were given 1,2,4-triazole by gavage at a dose of 0, 5, 15, 30 or 45 mg/kg bw/d from gestational days 6 to 28.

At the highest dose, 5 out of 25 females were sacrificed between gestational day 16 and 24 due to their moribund condition which consisted of severely decreased food consumption and bw already observed at gestational day 7, decreased motor activity, soft and/or liquid faeces. Among surviving rabbits, there were no significant changes on bw, food consumption and gross pathology. At the end of the exposure period (GD 29), the bw was of 4.04, 3.95, 3.93, 4.00 and 3.76 kg at 0, 5, 15, 30 and 45 mg/kg bw/d, respectively. During the organ weight examination, a significant decrease of gravid uterine weight was observed at the highest dose (0.56, 0.54, 0.51, 0.53 and 0.46** kg respectively at 0, 5, 15, 30 and 45 mg/kg bw/d).

Table 34 : bw data (Hoberman, 2004, cited in JMPR, 2008)

	0 mg/kg bw/d	5 mg/kg bw/d	15 mg/kg bw/d	30 mg/kg bw/d	45 mg/kg bw/d
Bw at GD29 (kg)	4.04	3.95	3.93	4.00	3.76
Gravid uterine weight (kg)	0.56	0.54	0.51	0.53	0.46**
Corrected maternal bw	3.48	3.40	3.42	3.46	3.31[a]

[a] : excludes values for rabbits that were moribund sacrificed or prematurely delivered

The litter averages for corpora lutea, implantations, litter size, live fetuses, dead fetuses, early and late resorptions, percent of dead or resorbed conceptuses, and percent live male fetuses were comparable among all groups (See table 35).

Table 35 : Litter observations (Hoberman, 2004, cited in JMPR, 2008)

	0 mg/kg bw/d	5 mg/kg bw/d	15 mg/kg bw/d	30 mg/kg bw/d	45 mg/kg bw/d
No. dams examined	25	24	24	25	19

Corpora lutea	9.8	9.8	9.9	10.2	9.8
Implantations	9.0	9.0	8.8	9.3	9.0
Early resorption (n)	1	2	4	10	6
Late resorption (n)	7	8	7	3	8
Litter size (n)	8.7	8.6	8.3	8.8	8.3
Live fetuses (n)	217	207	199	218	157
Dead fetuses (n)	0	0	0	1	0
Percent of dead or resorbed conceptuses	3.1	4.7	4.8	6.4	7.0
Percent live male fetuses	59.0	56.9	53.2	56.6	60.6

Concerning the fetal observations, bw were significantly lower at the highest dose than the control group (See table 36). Up to 30 mg/kg bw/d, no gross external, soft tissue or skeletal fetal alterations were observed. However, at 45 mg/kg bw/d, a few alterations of the urogenital system were detected. At this dose, 3 fetuses from 1 litter had one or two low set and small kidneys, 2 fetuses from 2 litters had an absent kidney.

Table 36 : Fetal observation (Hoberman, 2004, cited in JMPR, 2008)

	0 mg/kg bw/d	5 mg/kg bw/d	15 mg/kg bw/d	30 mg/kg bw/d	45 mg/kg bw/d
Live fetal bw (in g)	44.35	43.42	43.82	42.48	39.46**
Male bw (in g)	44.92	43.91	44.25	42.39	39.65**
Female bw (in g)	42.92	42.79	43.64	42.20	38.70*

* $p < 0.05$ **$p<0.01$

Based on the results of the study, the NOAEL for maternal and developmental toxicity was 30 mg/kg bw/d.

In a two-generation reproductive toxicity study following OECD guideline 416 (Young A.D. and Sheets L.P., 2005), groups of 30 male and 30 female rats were given diets containing 1,2,4-triazole at a concentration of 0, 250, 500 or 3000 ppm (See table 37 for the dosing in mg/kg bw/d during the different exposure period). The exposure period began 10 weeks before mating, and continued through mating, gestation, and lactation.

Table 37 : Dose level by group in mg/kg bw/d (Young A.D. and Sheets L.P., 2005)

	Phase of study	250 ppm in mg/kg bw/d	500 ppm in mg/kg bw/d	3000 ppm in mg/kg bw/d
♂	Premating (P-gen)	15.4	30.9	188.6
	Premating (F1-gen)	16	32	NA
♀	Premating (P-gen)	17.5	36.2	217.9
	Gestation (P-gen)	18.6	38.6	231.7[a]
	Lactation (P-gen)	19.3	38.7	NA
	Premating (F1-gen)	18.9	37.5	NA
	Gestation (F1-gen)	17.4	34.4	NA
	Lactation (F1-gen)	20.3	35.8	NA

[a] *: based on only 2 pregnant females*

No treatment-related effects were observed concerning deaths or clinical signs at any dietary dose level. Bw of males and females was statistically modified during different exposure periods (see table 38).

Table 38 : Body weight data in grams for P and F1 animals (Young A.D. and Sheets L.P., 2005)

	Phase of study	0 ppm	250 ppm	500 ppm	3000 ppm
♂	P adults (D119)	477.5	465.1	460.6	426.6**
	F1 adults (D98)	461.9	435.2*	428.4**	/
♀	P premating-mating (D70)	244.1	244.9	239.5	233.4*
	P gestation (D20)	345.3	340.9	340.0	284.7**[a]
	P lactation (D21)	284.2	287.4	287.4	/
	F1 premating-mating (D70)	236.2	227.5	230.8	/
	F1 gestation (D20)	323.8	313.3	311.8	/
	F1 lactation (D21)	281.4	267.8*	271.2	/

[a] : based only on 2 dams; * $p < 0.05$ **$p<0.01$

Males and females of the F0-generation at the highest dose had a significantly lower terminal bw (473.1/277.2, 460.7/283.1, 456.1/280.9 and 419.4*/245.1* g at 0, 250, 500 and 3000 ppm in males/females, respectively) and lower absolute brain weight (2.092/1.955, 2.075/1.941, 2.044/19.51 and 2.006*/1.853* g respectively at 0, 250, 500 and 3000 ppm in males/females) compared with the control group. Several other organs also showed modifications at this highest dose such as ovaries (0.058/0.058, 0.059/0.057, 0.055/0.054 and 0.067*/0.071* g (left/right ovaries) at 0, 250, 500 and 3000 ppm, respectively), thyroid, liver. In addition to the brain weight change, minimal to marked degeneration/necrosis was observed in 30 out of 30 males and in 28 out of 30 females. Moreover, in the ovaries, changes in number of total corpora lutea were observed (24.9, 23.0, 15.6 and 41.3 respectively at 0, 250, 500 and 3000 ppm). Furthermore, the histopathological examination of uterus revealed a higher incidence of dilatation (14* females at 3000 ppm vs 4 females in control).

For litters of 250 and 500 ppm dose level, live birth, viability, mean litter sizes, sex ratios and clinical signs were not modified in the treated compared to the control groups. Furthermore, the gross necropsy was similar between all dose levels.

Bw and bwg changes were not observed in pups at the F1-generation however the bw at the F2-generation examined at PND 0 and 21 were reduced compared with control. (See table 39)

Table 39 : Body weight of pups in the F1 and F2-generation (number of litters) (Young A.D. and Sheets L.P., 2005)

		F1-generation				F2-generation		
		0 ppm	250 ppm	500 ppm	3000 ppm	0 ppm	250 ppm	500 ppm
D0	♂	6.3	6.0	6.2	/	6.3	6.0*	5.8**
	♀	6.0	5.6	5.9	5.4	6.0	5.6**	5.5*
	♂ + ♀	6.2 (22)	5.9 (25)	6.1 (25)	5.4 (2)	6.2 (27)	5.8** (26)	5.7** (25)
D7	♂	17.0	16.1	16.2	/	16.9	16.1	16.1
	♀	16.1	15.5	15.4	9.1**	16.3	15.6	15.8
	♂ + ♀	16.5 (22)	15.8 (25)	15.7 (25)	9.1** (2)	16.6 (27)	15.9 (26)	16.0 (24)
D21	♂	52.0	50.2	50.5	/	51.2	47.5**	48.4*

	♀	49.4	47.9	47.6	/	49.4	45.9**	46.7*
	♂ + ♀	50.7 (22)	49.1 (25)	48.4 (25)	/	50.2 (27)	46.8** (26)	47.6* (24)

According to the results, the NOAEL for the parental toxicity was 500 ppm based on lower bw and degenerative findings observed in the cerebellum at the highest dose level. The NOAEL for fertility could not be determined based on the reduction in testicular sperm counts noted at 250 ppm. Moreover, the NOAEL for developmental toxicity was set at 500 ppm which was the highest dose allowing assessment of the developmental effects as the 3000 ppm dose level was not further examined due to the low number of pups.

10.10.6 Comparison with the CLP criteria

As there are no epidemiological studies available, Cat. 1A is not warranted.

Category 2 is not supported as we consider the evidence strong enough to warrant a classification in cat. 1B as it is shown below.

According to the CLP Regulation (EC No 1272/2008) the classification of a substance in category 1B for reproductive toxicants *"is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate".*

Developmental disturbances were observed in a developmental toxicity study performed in rats (Renhof M., 1988a). This study indicated an increased incidence of cleft palates (in 3/25 litters (12% litter incidence) at 200 mg/kg bw/d). In comparison with historical control data (1986-1989) only one case of cleft palate was reported in the year 1987 (litter incidence 4.17%) and only one case in 1989 (litter incidence 7.69%). Moreover, the high rate of resportions (53%) observed at this highest dose may have masked the number of malformations, which are known to be very rare in rats. Additionally, in males, the incidence of cryptorchism was above the historical values at the treated dose group (100 and 200 mg/kg) in this developmental toxicity study in rats (in 2/253, 11/226 and 6/138 pups respectively at 0, 100 and 200 mg/kg bw/d) and an increase of pre and post-implantation losses was observed (number of implantation loss per dam : 0.5, 0.3 and 6.3** respectively at 0, 100 and 200 mg/kg bw/d). In conjunction, the mean number of foetus per dams was significantly decreased. Finally, a significant dose-related decrease in mean foetus weight was seen at 100 and 200 mg/kg bw/d. These severe effects are not explained by the maternal toxicity as the bw change appear only at the highest dose level

Furthermore, in the other developmental toxicity study performed in rats (Renhof M., 1988b) a significant increased incidence of runts was noted at the highest dose level (100 mg/kg bw/d). In addition, the mean foetus weight was significantly decreased at 100 mg/kg bw/d compared to the control group. However, these effects appear at the same dose level as the bw modification.

In the prenatal developmental toxicity study in rabbits (Hoberman, 2004), an important increase in the mortality rate (20%) was observed at the highest dose (45 mg/kg bw/d). However, a dose-related increase in the incidence of dead or resorbed conceptuses per litter was already observed at 30 mg/kg bw/d (3.1, 4.7, 4.8, 6.4 and 7.0 respectively at 0, 5, 15, 30 and 45 mg/kg bw/d). This examination may have masked the number of malformations.

No conclusion about developmental toxicity can be drawn from the 2-generation toxicity study (Yound A.D. and Sheets L.P., 2005) as the severe decrease in the fertility index at 3000 ppm (corresponding to less than 235 mg/kg bw/d) lead to a premature termination of this dose level. Consequently, the highest dose for the F1-generation was 500 ppm corresponding to less than 40 mg/kg bw/d. Thus, a concern cannot be excluded.

According to all these severe effects, a classification as Repr. 1B for adverse effects on development is warranted.

10.10.7 Adverse effects on or via lactation

10.10.7.1 Non-human information

No information available

10.10.7.2 Human information

No information available

10.10.7.3 Other relevant information

No information available

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

NA

10.10.9 Comparison with the CLP criteria

NA

10.10.10 Conclusion on classification and labelling for reproductive toxicity

According to all of these available studies which revealed severe reproductive effects (in more than 1 species) as mentioned above, a classification as Repr. 1B; H360FD is warranted.

Furthermore during the MSC-54, it was concluded that the best way forward for 1,2,4-triazole was the submission of a CLH dossier for reproductive toxicity, more particular Repro. 1B, H360FD.

10.11 Specific target organ toxicity-single exposure

Not evaluated in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Not evaluated in this dossier.

10.13 Aspiration hazard

Not evaluated in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this dossier.

13 ADDITIONAL LABELLING

Not relevant.

14 ABBREVIATIONS

* : p<0.05, statistically significant

** : p<0.01, statistically significant

♂ : male

♀ : female

bw : body weight

bwg : body weight gain

Calc. : Calcium

Cl : chloride

D : day

FOB : functional observational battery

GD : gestational day

Hct : hematocrit

HDW : haemoglobin distribution width

Hgb : hemoglobin

K : potassium

MCH : mean cell hemoglobin

MCV : mean cell volume

NA : not applicable

ND : not determined

NE : not examined

NOAEL : no observed adverse effect level

PND : post-natal day

RDW : red cell distribution width

Trigl. : triglyceride

TSH : thyroid stimulating hormone

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16 ANNEXES

- *Annex I to CLH report*
- *Confidential annex to the CLH report*