Annex I to the 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

Contact details for dossier submitter:

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1 PHYSICAL HAZARDS

Not evaluated in this dossier.

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated in this dossier.

3 HEALTH HAZARDS

3.1 Acute toxicity – oral route

3.1.1.1 Acute oral toxicity

Study reference:

US EPA HPV Challenge Program, Test plan submission, July 2009, 1H-1,2,2-triazole CAS No 288-88-0

Detailed study summary and results:

Test type

According to OECD Guideline 401

Test substance

- *1,2,4-triazole*
- *Degree of purity : > 98%*
- *Batch number : Z81429*

Test animals

- *Species/strain/sex : Rat/Wistar/ male and female*
- *No. of animals per sex per dose : 5/sex/dose*

Administration/exposure

- *Mode of administration (gavage, in diet, other) : oral : gavage*
- *Doses/concentration levels : 1000, 1500 and 2000 mg/kg bw*
- *Post exposure observation period : 15 days*
- *Control group and treatment : no data*
- *Vehicle: bi-distilled water*

Results and reliability

- LD50 or LC50 value with confidence limits if calculated : 1320.39 mg/kg bw
- Number of deaths at each dose level : 1000mg/kg bw : no mortality

  In males : at 1500 mg/kg bw, 2 rats died after 24h and 2 after 2d and at 2000 mg/kg bw, 4 died after 24h and 1 after 2d.

  In females : at 1500 mg/kg bw, 3 rats died after 24h and 2 after 3d and at 2000 mg/kg bw, 4 died after 24h and 1 after 2d.

- Clinical signs: ≥ 1000 mg/kg : sedated, ventral recumbency, dyspnea
- Necropsy findings, including doses affected, severity and number of animals affected : No data available

3.1.2 Acute oral toxicity

Study reference:

Thyssen and Kimmerle, 1976. Cited in JMPR, 2008

Detailed study summary and results:

Test type

According to OECD Guideline 423

Test substance

- *1,2,4-triazole*

Test animals

- *Species/strain/sex : Rat/Wistar/ male and female*
- *No. of animals per sex per dose : 15rats/sex/dose : 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*

Administration/exposure

- *Mode of administration (gavage, in diet, other) : oral : gavage*
- *Doses/concentration levels : 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*
- *Post exposure observation period : 14 days*
- *Control group and treatment : no data*
- *Vehicle: distilled water and Cremophor EL*

Results and reliability

- *LD50 or LC50 value with confidence limits if calculated :*

  LD50 (females) : 1648 mg/kg

  LD50 (males) : 1650 mg/kg
- *Number of deaths at each dose level : no data*
- *Time of death (provide individual animal time if less than 24 hours after dosing) : no information available*
- *Clinical signs: reduction in general well-being, sedation, breathing disorders*
- *Necropsy findings : no major changes*

3.1.3 Acute oral toxicity

Study reference:

Procopio and Hamilton, 1992. Cited in JMPR, 2008

Detailed study summary and results:

Test type

According to OECD Guideline 423

Test substance

- *1,2,4-triazole*

Test animals

- *Species/strain/sex : Rat/Crl:CD BR/ male*
- *No. of animals per sex per dose : 3 male/dose*

Administration/exposure

- *Mode of administration (gavage, in diet, other) : oral : gavage*
- *Doses/concentration levels : 500 and 5000 mg/kg bw*
- *Control group and treatment : no*
- *Vehicle: methylcellulose*

Results and reliability

- *LD50 or LC50 value with confidence limits if calculated : > 500 - < 5000 mg/kg bw*
- *Number of deaths at each dose level : at 500 mg/kg bw no death and at 5000 mg/kg bw all rats died*
- *Time of death (provide individual animal time if less than 24 hours after dosing) : at 5000 mg/kg bw all rats died within 10 min*
- *Clinical signs: no effects*
- *Necropsy findings : 5000 mg/kg : reddened duodenum and reddened glandular portion of stomach*

3.2 Acute toxicity - dermal route

Not evaluated in this dossier.

3.3 Acute toxicity - inhalation route

Not evaluated in this dossier.

3.4 Skin corrosion/irritation

Not evaluated in this dossier.

3.5 Serious eye damage/eye irritation

Not evaluated in this dossier.

3.6 Respiratory sensitisation

Not evaluated in this dossier.

3.7 Skin sensitisation

Not evaluated in this dossier.

3.8 Germ cell mutagenicity

Not evaluated in this dossier.

3.9 Carcinogenicity

Not evaluated in this dossier.

3.10 Reproductive toxicity

3.10.1 Animal data

3.10.1.1 A two-generation reproductive toxicity study in rats

Study reference:

Young A.D. and Sheets L.P., 2005

Detailed study summary and results:

Test type

Following OECD TG 416

Following US EPA guideline : OPPTS 870.3800

Following GLP regulation

Test substance

- *1,2,4-triazole*
- *Degree of purity : ≥ 99.9 %*
- *Batch number : S13691*

Test animals

- *Species/strain/sex : Rats / Wistar Hannover / both sexes*
- *No. of animals per sex per dose : 30/sex/dose*
- *Age and weight at the study initiation : 9.5 weeks of age at the beginning of exposure*

Administration/exposure

- *Route of administration : oral (diet)*
- *duration and frequency of test/exposure period : P-gen and F1-gen : 10 weeks of premating period until lactation D21, daily*
- *doses/concentration levels : 0, 250, 500 and 3000 ppm corresponding to :*

	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*

- *vehicle: ethanol*

Description of test design:

- *details on mating procedure : mating was accomplished by co-housing one female with one male for up to 14 days. During this phase, vaginal smears were collected each morning to examine the presence or absence of sperm and/or the internal vaginal plug.*
- *premating exposure period for males and females (P and F1) : 10 weeks*
- *standardization of litters : yes. On lactation D4, each litter was adjusted (4 males and 4 females) by random selection*
- *parameters assessed for P and F1*
    - *oestrous cycle evaluation : during a 3-w period prior mating period*
    - *sperm examination : yes*

Results and discussion

NOAEL (parental toxicity) : 500 ppm based on lower bw and degenerative findings observed in the cerebellum at the highest dose level

NOAEL (fertility) : < 250 ppm based on the reduction in testicular sperm counts noted at 250 ppm

NOAEL (developmental toxicity) : 500 ppm which was the highest dose allowing assessment of the developmental effects as the 3000 ppm dose level had been stopped due to the low number of pups

For P and F1 adults (per dose):

- *time of death during the study and whether animals survived to termination : no mortality observed during the study*
- *body weight data (in grams) for P and F1 animals :*

	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

- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :*
  - *P-gen : ♂ : absolute weight :*

Weight (in g)	*Term. Bw*	*brain*	*Liver*	*Sem.Ves.*	*TestisL*	*TestisR*	*Epid.L*	*EpidiR*
0 ppm	*473.1*	*2.092*	*16.482*	*1.605*	*1.837*	*1.983*	*0.739*	*0.772*
250 ppm	*460.7*	*2.075*	*16.225*	*1.593*	*1.759*	*1.848*	*0.733*	*0.740*
500 ppm	*456.1*	*2.044*	*15.968*	*1.673*	*1.878*	*1.893*	*0.763*	*0.781*
3000 ppm	*419.4**	*2.006**	*15.220*	*1.616*	*1.827*	*1.793*	*0.735*	*0.737*

* p < 0.05

Relative weight :

Weight	*Term. bw*	*brain*	*Liver*	*Sem.Ves.*	*TestisL*	*TestisR*	*Epid.L*	*EpidiR*
0 ppm	*473.1*	*0.445*	*3.470*	*0.341*	*0.387*	*0.422*	*0.156*	*0.163*
250 ppm	*460.7*	*0.452*	*3.522*	*0.347*	*0.381*	*0.402*	*0.159*	*0.161*
500 ppm	*456.1*	*0.451*	*3.504*	*0.368*	*0.413*	*0.417*	*0.168*	*0.172*
3000 ppm	*419.4**	*0.483**	*3.630*	*0.384**	*0.440**	*0.431*	*0.176**	*0.176**

* p < 0.05

  - *P-gen : ♀ : absolute weigh :*

Weight (in g)	*Term. bw*	*Brain*	*Liver*	*Uterus*	*OvaryL*	*OvaryR*
0 ppm	*277.2*	*1.955*	*11.296*	*0.625*	*0.058*	*0.058*
250 ppm	*283.1*	*1.941*	*11.959*	*0.594*	*0.059*	*0.057*
500 ppm	*280.9*	*1.951*	*12.211*	*0.594*	*0.055*	*0.054*

3000 ppm	*245.1**	*1.853**	*9.021**	*0.603*	*0.067**	*0.071**

* p < 0.05

Relative weight :

Weight	*Term. bw*	*Brain*	*Liver*	*Uterus*	*OvaryL*	*OvaryR*
0 ppm	*277.2*	*0.710*	*4.061*	*0.227*	*0.021*	*0.021*
250 ppm	*283.1*	*0.688*	*4.210*	*0.211*	*0.021*	*0.020*
500 ppm	*280.9*	*0.698*	*4.331*	*0.214*	*0.020*	*0.019*
3000 ppm	*245.1**	*0.758**	*3.679**	*0.247*	*0.028**	*0.029**

* p < 0.05

- *F1-gen : ♂ : absolute weight :*

Weight (in g)	*Term. bw*	*Brain*	*Liver*	*Sem.Ves.*	*TestisL*	*TestisR*	*Epid.L*	*EpidiR*
0 ppm	*464.5*	*2.066*	*15.897*	*1.506*	*1.899*	*1.879*	*0.739*	*0.711*
250 ppm	*440.8**	*2.032*	*15.461*	*1.424*	*1.803*	*1.856*	*0.714*	*0.699*
500 ppm	*426.6**	*2.002**	*14.905*	*1.481*	*1.830*	*1.818*	*0.719*	*0.706*

* p < 0.05

Relative weight :

Weight	*Term. bw*	*Brain*	*Liver*	*Sem.Ves.*	*TestisL*	*TestisR*	*Epidi.L*	*Epidi.R*
0 ppm	*464.5*	*0.447*	*3.420*	*0.328*	*0.411*	*0.407*	*0.160*	*0.154*
250 ppm	*440.8**	*0.463*	*3.513*	*0.320*	*0.411*	*0.423*	*0.162*	*0.159*
500 ppm	*426.6**	*0.472**	*3.489*	*0.349*	*0.432*	*0.429*	*0.169*	*0.167*

* p < 0.05

- *F1-gen : ♀ : absolute weight :*

Weight (in g)	*Term. bw*	*brain*	*Liver*	*Uterus*	*OvaryL*	*OvaryR*
0 ppm	*277.2*	*1.930*	*12.191*	*0.567*	*0.054*	*0.052*
250 ppm	*262.9**	*1.888*	*11.263*	*0.554*	*0.052*	*0.054*
500 ppm	*265.7*	*1.881*	*11.489*	*0.606*	*0.054*	*0.053*

* p < 0.05

Relative weight :

Weight (in g)	*Term. bw*	*brain*	*Liver*	*Uterus*	*OvaryL*	*OvaryR*
0 ppm	*277.2*	*0.700*	*4.369*	*0.210*	*0.019*	*0.019*
250 ppm	*262.9**	*0.720*	*4.275*	*0.212*	*0.020*	*0.021*
500 ppm	*265.7*	*0.711*	*4.308*	*0.230*	*0.020*	*0.020*

* p < 0.05

- *effects on sperm :*
  - *Sperm motility :*

	Doses (N)	*Mean % motility*	*Mean % progressive*
P-gen	*0 ppm (28)*	*76.2*	*55.9*
	250 ppm (27)	*78.9*	*56.5*
	500 ppm (30)	*78.9*	*56.4*
	3000 ppm (29)	*78.9*	*57.3*
F1-gen	*0 ppm (29)*	*87.1*	*63.9*
	250 ppm (29)	*87.8*	*65.7*
	500 ppm (29)	*89.5*	*67.6*

- *Total sperm count :*

	Doses (N)	*Epididymis (mean)*	*Testis (mean)*
P-gen	*0 ppm (28)*	*58.2*	*72.0*
	250 ppm (27)	*57.0*	*63.1**
	500 ppm (29)	*65.7*	*64.4*
	3000 ppm (28)	*43.2**	*61.2**
F1-gen	*0 ppm (29)*	*49.2*	*69.2*
	500 ppm (29)	*48.6*	*68.3*

* $p < 0.05$

- *Sperm morphology :*

	Doses (N)	*Mean % normal*	*Mean % abnormal*	*Mean % detached*
P-gen	*0 ppm (28)*	*98.7*	*0.8*	*0.5*
	250 ppm (27)	*98.1*	*1.0*	*0.8*
	500 ppm (29)	*97.0**	*1.4**	*1.6**
	3000 ppm (29)	*95.7**	*1.5**	*2.8**
F1-gen	*0 ppm (29)*	*98.1*	*1.1*	*0.8*
	500 ppm (29)	*97.9*	*1.4*	*0.7*

* $p < 0.05$

- *number of P and F1 females cycling normally and cycle length :*
  - *number of estrous cycle :*

    In P-gen : 3.6, 3.8, 3.4 and 3.6 respectively at 0, 250, 500 and 3000 ppm

    In F1-gen : 3.7, 3.7 and 3.8 respectively at 0, 250 and 500 ppm
  - *Estrous cycle length :*

    In P-gen : 4.2, 4.2, 4.4 and 4.2 respectively at 0, 250, 500 and 3000 ppm

    In F1-gen : 4.1, 4.1 and 4.1 respectively at 0, 250 and 500 ppm
- *Number of animals mated, number of animals with implants, mating index, fertility index :*
  - *In P-gen :*

	0 ppm	*250 ppm*	*500 ppm*	*3000 ppm*
Number of animals mated	*30*	*30*	*29*	*28*
Number of animals with implants	*23*	*25*	*25*	*2*
Mating index	*100.0*	*100.0*	*96.7*	*93.3*
Fertility index	*76.7*	*83.3*	*86.2*	*7.1***

** $p < 0.01$

- *In F1-gen :*

	0 ppm	*250 ppm*	*500 ppm*
Number of animals mated	*30*	*30*	*29*
Number of animals with implants	*28*	*26*	*25*
Mating index	*100.0*	*100.0*	*96.7*
Fertility index	*93.3*	*86.7*	*86.2*

- *duration of gestation (calculated from day 0 of pregnancy) :*

  In P-gen : 22.3, 22.0, 22.2 and 23.5 days respectively at 0, 250, 500 and 3000 ppm

  In F1-gen : 22.1, 21.9 and 21.8 days respectively at 0, 250, and 500 ppm

- *number of implantations, corpora lutea, litter size :*
  - *Total number of implantations : in P-gen : 265, 310, 279 and 3 respectively at 0, 250, 500 and 3000 ppm*

    in F1-gen : 304, 300, 273 respectively at 0, 250 and 500 ppm

- *histopathological findings: a few organs were affected :*
  - *cerebellum : at 3000 ppm in the P-generation, a mild to moderate degeneration/necrosis was observed. Moreover, a loss of Purkinje cells, white matter degeneration and gliosis were noted.*
  - *ovaries : at the P-generetaion, a statistically significant higher number of total corpora lutea were noted at the highest dose level.*
  - *uterus : an increased incidence of uterine horn dilatation was observed in the P-generation at 3000 ppm.*

For F1 and F2 pups/litters (per dose):

- *mean number of live pups (litter size) :*
  - *F1-pups : Total No. of pups born : 233, 279, 260, 2 respectively at 0, 250, 500 and 3000 ppm.*

    Litter size : 10.6, 11.2, 10.4, 1.0 respectively at 0, 250, 500 and 3000 ppm.
  - *F2-pups : Total No. of pups born : 280, 287, 260 respectively at 0, 250 and 500 ppm*

Litter size : 10.4, 11.0, 10.4 respectively at 0, 250 and 500 ppm

- *Pup clinical observation : no treatment-related effects*
- *sex ratio : Sex distribution at birth (% males)*
  - *F1-pups : 54.1, 55.4, 50.7, 0.0 respectively at 0, 250, 500 and 3000 ppm.*
  - *F2-pups : 48.7, 47.3, 40.6 respectively at 0, 250 and 500 ppm*
- *viability index :*
  - *F1-pups : 96.2, 97.1, 99.6, 100.0 respectively at 0, 250, 500 and 3000 ppm.*
  - *F2 pups : 99.7, 98.8, 95.6 respectively at 0, 250 and 500 ppm*
- *mean litter or pup weight by sex and with sexes combined :*
  - *F1-pups body weight in grams (number of litters) :*

		0 ppm	*250 ppm*	*500 ppm*	*3000 ppm*
D0	♂	*6.3 (22)*	*6.0 (25)*	*6.2 (24)*	*/*
	♀	*6.0 (22)*	*5.6 (25)*	*5.9 (25)*	*5.4 (2)*
	♂ + ♀	*6.2 (22)*	*5.9 (25)*	*6.1 (25)*	*5.4 (2)*
D7	♂	*17.0 (21)*	*16.1 (25)*	*16.2 (24)*	*/*
	♀	*16.1 (22)*	*15.5 (25)*	*15.4 (25)*	*9.1** (2)*
	♂ + ♀	*16.5 (22)*	*15.8 (25)*	*15.7 (25)*	*9.1** (2)*
D21	♂	*52.0 (21)*	*50.2 (25)*	*50.5 (24)*	*/*
	♀	*49.4 (22)*	*47.9 (25)*	*47.6 (25)*	*/*
	♂ + ♀	*50.7 (22)*	*49.1 (25)*	*48.4 (25)*	*/*

** p < 0.01

  - *F2-pups body weight in grams (number of litters) :*

		0 ppm	*250 ppm*	*500 ppm*
D0	♂	*6.3 (26)*	*6.0* (26)*	*5.8** (23)*
	♀	*6.0 (27)*	*5.6** (26)*	*5.5* (25)*
	♂ + ♀	*6.2 (27)*	*5.8** (26)*	*5.7** (25)*
D7	♂	*16.9 (26)*	*16.1 (26)*	*16.1 (22)*
	♀	*16.3 (27)*	*15.6 (26)*	*15.8 (24)*
	♂ + ♀	*16.6 (27)*	*15.9 (26)*	*16.0 (24)*
D21	♂	*51.2 (26)*	*47.5** (26)*	*48.4* (22)*
	♀	*49.4 (27)*	*45.9** (26)*	*46.7* (24)*
	♂ + ♀	*50.2 (27)*	*46.8** (26)*	*47.6* (24)*

* p < 0.05 **p < 0.01

- *Preputial separation :*
  - *F1-pups : 40.7, 41.2, 41.3 respectively at 0, 250 and 500 ppm*

- *F2-pups : 40.7, 41.8*, 41.5 respectively at 0, 250 and 500 ppm*

- *Vaginal opening :*
  - *F1-pups : 33.4, 35.3**, 35.0* respectively at 0, 250 and 500 ppm*
  - *F2-pups :33.6, 34.9, 34.2 respectively at 0, 250 and 500 ppm*
- *Anogenital distance : F2-pups : ♂ : 3.5, 3.5, 3.4 respectively at 0, 250 and 500 ppm*

  ♀ : 1.8, 1.6, 1.6 respectively at 0, 250 and 500 ppm
- *Micropathology evaluation : no treatment-related effects*

3.10.1.2 An embryotoxicity study performed in rats

Study reference:

Renhof M., 1988a (cited in JMPR, 2008)

Detailed study summary and results:

Test type

Following EPA OPPTS 83-3 guidance

Following GLP regulation

Test substance

- *1,2,4-Triazole*
- *Degree of purity : 94.0 %*
- *Batch number : 270184*

Test animals

- *Species/strain/sex : Rat / Bor : Wisw (SPF Cpb) / female*
- *No. of animals per sex per dose : 25 inseminated females*
- *Age and weight at the study initiation : weight : between 181 and 228 g, sexually mature, nulliparous*

Administration/exposure

- *Route of administration : oral (with stomach tube)*
- *duration and frequency of test/exposure period : GD 6 - 15, daily*
- *doses/concentration levels : 0, 100 and 200 mg/kg bw/d*
- *vehicle: cremophor-EL emulsion 0.5 %*

Results and discussion

NOAEL (maternal toxicity) : 100 mg/kg bw/d

NOAEL (developmental toxicity) : < 100 mg/kg bw/d

For dams :

- *number of animals at the start of the test : 25/dose*
- *Mortality : no mortality observed*

- *Clinical observation : no effects*
- *body weight data (in g):*

	0 mg/kg bw/d	*100 mg/kg bw/d*	*200 mg/kg bw/d*
BW at GD 0	*204.6*	*203.8*	*203.2*
BW at GD 6	*221.5*	*222.5*	*220.3*
BW at GD 15	*250.9*	*249.8*	*241.8*
BW at GD 20	*301.4*	*295.7*	*263.6*
Adjusted maternal bwg	*30.8*	*34.16*	*33.24*

- *body weight gain :*
  - *during administration period : 29.3, 27.4 and 21.5* g respectively at 0, 100 and 200 mg/kg bw/d*
  - *during entire pregnancy : 96.9, 91.9 and 60.4** g respectively at 0, 100 and 200 mg/kg bw/d*
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals : no information available*
- *Insemination and fertilisation :*

	Number of inseminated ♀	*Fertilised ♀*		*Pregnant ♀*	
		number	*%*	*number*	*%*
0 mg/kg bw/d	*25*	*21*	*84.0*	*21*	*100.0*
100 mg/kg bw/d	*25*	*19*	*76.0*	*19*	*100.0*
200 mg/kg bw/d	*25*	*25*	*100.0*	*25*	*100.0*

- *haematological and clinical biochemistry findings : no information available*
- *number of implantations, corpora lutea, litter size :*

		0 mg/kg bw/d	*100 mg/kg bw/d*	*200 mg/kg bw/d*
Mean number of implantations per dams		*12.5*	*12.2*	*11.8*
Mean number of corpora lutea per dams		*13.6*	*13.9*	*14.2**
Mean number of foetus per dams	♂	*5.9*	*6.0*	*3.1***
	♀	*6.1*	*5.9*	*2.4***
	Total	*12.0*	*11.9*	*5.5***

* p < 0.05 ** p < 0.01

- *number of dams with abortions, early deliveries, stillbirths, resorptions and/or dead foetuses :*

		0 mg/kg bw/d	*100 mg/kg bw/d*	*200 mg/kg bw/d*
% resorption	*Early*	*0.381*	*0.316*	*0*
	Late	*3.381*	*2.474*	*52.36*

Mean number of foetus loss per dams	*0.5*	*0.3*	*6.3***
Mean runts	*0.24*	*2.84**	*4.96***

** p < 0.01

- *mean gravid uterine weight (in g) : 66, 57.737 and 27.16 g respectively at 0, 100 and 200 mg/kg bw/d*

For foetus (per dose):

- *Total number of foetus : 253, 226 and 138 respectively at 0, 100 and 200 mg/kg bw/d*
- *mean number pups (litter size) and sex ratio :*

		0 mg/kg bw/d	*100 mg/kg bw/d*	*200 mg/kg bw/d*
Mean number of foetus per dams	♂	*5.9*	*6.0*	*3.1***
	♀	*6.1*	*5.9*	*2.4***
	Total	*12.0*	*11.9*	*5.5***

** p < 0.01

- *mean foetus weight and placental weight (in g) :*

	0 mg/kg bw/d	*100 mg/kg bw/d*	*200 mg/kg bw/d*
Mean placental weight	*0.59*	*0.52***	*0.49***
Mean foetus weight	*3.55*	*3.06***	*2.35***

** p < 0.01

- *Malformation : incidence of malformation :*

	0 mg/kg bw/d	*100 mg/kg bw/d*	*200 mg/kg bw/d*	*HCD*
Undescended testicule	*2*	*11*	*6*	*/*
Cleft palate	*0*	*0*	*4*	*/*
hydronephrosis	*1*	*1*	*7*	*1*

HCD : incidence of spontaneous malformation in control group (year 1985)

3.10.1.3 An embryotoxicity study performed in rats

Study reference:

Renhof M., 1988b (cited in JMPR, 2008)

Detailed study summary and results:

Test type

Following EPA OPPTS 83-3

Following GLP regulation

Test substance

- *1,2,4-triazole*
- *Degree of purity : 95.3 %*

- *Batch number : 270/84*

Test animals

- *Species/strain/sex : Rats / Bor : wisw (SPF Cpb) / female*
- *No. of animals per sex per dose : 25 inseminated females/group*
- *Age and weight at the study initiation : weight : 182 – 213 g, sexually mature, nulliparous*

Administration/exposure

- *Route of administration : oral*
- *duration and frequency of test/exposure period : GD 6 - 15, daily*
- *doses/concentration levels : 0, 10, 30 and 100 mg/kg bw/d*
- *vehicle : cremophor-EL emulsion 0.5%*
- *post exposure observation period : until GD 20*

Results and discussion

NOAEL (maternal toxicity) : 30 mg/kg bw/d

NOAEL (developmental toxicity) : 30 mg/kg bw/d

For dams (per dose):

- *number of animals at the start of the test and matings :*

		0 mg/kg bw/d	*10 mg/kg bw/d*	*30 mg/kg bw/d*	*100 mg/kg bw/d*
Inseminated females		*25*	*25*	*25*	*25*
Fertilised females	*Number*	*21*	*22*	*19*	*24*
	%	*84.0*	*88.0*	*76.0*	*96.0*
Pregnant females	*Number*	*21*	*22*	*19*	*24*
	%	*100*	*100*	*100*	*100*

- *time of death during the study and whether animals survived to termination : no mortality observed during the study*
- *body weight data : BWG (in grams)*

	0 mg/kg bw/d	*10 mg/kg bw/d*	*30 mg/kg bw/d*	*100 mg/kg bw/d*
During exposure period	*28.2*	*25.4*	*26.8*	*21.8**
During entire pregnancy	*92.9*	*86.6*	*90.0*	*79.8**

* $p < 0.05$

- *body weight at sacrifice and absolute and relative organ weight data : no information available*
- *clinical observations: no effects*

- *number of implantations, corpora lutea, litter size : number of implantations per dams : 11.6, 10.5, 11.4, 10.6 respectively at 0, 10, 30 and 100 mg/kg bw/d*
- *number of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses : increased incidence of runts at the highest dose : mean runts : 0.33, 0.23, 0.53, 2.21* respectively at 0, 10, 30 and 100 mg/kg bw/d*

For foetus (per dose):

- *mean number of live pups (litter size) :*

  total number of foetus : 231, 222, 202, 228 respectively at 0, 10, 30 and 100 mg/kg bw/d

  Number of foetuses per dam : 11.0, 10.1, 10.6, 9.5 respectively at 0, 10, 30 and 100 mg/kg bw/d
- *sex ratio :*

  Number of male foetuses per dam : 6.5, 5.1, 6.0, 5.0* respectively at 0, 10, 30 and 100 mg/kg bw/d*

  Number of female foetuses per dam : 4.5, 5.0, 4.6, 4.5 respectively at 0, 10, 30 and 100 mg/kg bw/d
- *mean litter or pup weight by sex and with sexes combined : significant lower foetal weight at 100 mg/kg bw/d : 3.58, 3.59, 3.53 and 3.25** g respectively at 0, 10, 30 and 100 mg/kg bw/d*
- *external, soft tissue and skeletal malformations and other relevant alterations : foetuses with minor skeletal deviations : 2.00, 2.41, 2.84, 2.42 respectively at 0, 10, 30 and 100 mg/kg bw/d*

  Foetuses with malformations : 0.05, 0.05, 0.05, 0.17 respectively at 0, 10, 30 and 100 mg/kg bw/d

	0 mg/kg bw/d	*10 mg/kg bw/d*	*30 mg/kg bw/d*	*100 mg/kg bw/d*
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*

3.10.1.4 A developmental toxicity study in rats

Study reference:

Wickramaratne, 1987 (cited in JMPR, 2008)

Detailed study summary and results:

Test type

Non-guideline study

Non-GLP study

Test substance

- *1,2,4-triazole*
- *Degree of purity : no information available*
- *Batch number : no information available*

Test animals

- *Species/strain/sex : rat / Wistar / female pregnant*
- *No. of animals per sex per dose : 10 pregnant females/dose*
- *Age and weight at the study initiation : no information available*

Administration/exposure

- *Route of administration : oral*
- *duration and frequency of test/exposure period : GD 7 through 17*
- *doses/concentration levels : 0, 25 and 100 mg/kg bw/d*
- *historical control data if available : no information available*
- *vehicle: no information available*

Description of test design:

- *Examined maternal parameters were restricted to bw on gestational days 1, 7-17 and 22.*
- *Offspring observations were litter weight of live pups on PND 1 and 5 and number of live and dead pups on these days.*
- *Evaluation of malformations was not performed.*

Results and discussion

NOAEL (maternal toxicity) : 100 mg/kg bw/d

NOAEL (developmental toxicity) : 100 mg/kg bw/d

For dams (per dose):

- *body weight data : no effects (no more information available)*

For offspring (per dose):

- *mean number of live pups (litter size) : no effects (no more information available)*
- *viability index : no effects (no more information available)*

3.10.1.5 A developmental toxicity study performed in rabbits

Study reference:

Hoberman, 2004 (cited in JMPR, 2008)

Detailed study summary and results:

Test type

Prenatal developmental toxicity study

Following OECD TG 414 and US EPA OPPTS 870.3700

GLP

Test substance

- *1,2,4-triazole*
- *degree of purity : 99.9 %*
- *Batch number : S13691*

Test animals

- *Species/strain/sex : Rabbit / New Zealand White / pregnant female*
- *No. of animals per sex per dose : 25 / dose*
- *Age and weight at the study initiation : weight 2.7 – 4.4 kg, age : 5.5 months*

Administration/exposure

- *Route of administration : oral (stomach tube)*
- *duration and frequency of test/exposure period : GD 6 through 28 (sacrified at GD 29), daily*
- *doses/concentration levels : 0, 5, 15, 30, 45 mg/kg bw/d*
- *historical control data if available : no information available*
- *vehicle: aqueous 0.5% (w/w) carboxymethylcellulose (CMC)*

Results and discussion

NOAEL (maternal toxicity) : 30 mg/kg bw/d

NOAEL (developmental toxicity) : 30 mg/kg bw/d

For maternal (per dose) :

- *time of death during the study and whether animals survived to termination : at the highest dose, 5 females sacrified due to their moribund condition (between GD 16 - 24). No other mortality reported.*
- *Clinical observations : at the highest dose, a significantly increased incidence of decreased motor activity, clear perinasal substance, ptosis, excess salivation and hyperpnea were observed. Most of these signs occurred in does which were killed during the exposure period for their moribund condition.*
- *maternal body weight data : BWG was significantly decreased at 45 mg/kg bw/d*

	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*
Maternal bw at GD 29 (in kg)	*4.04*	*3.95*	*3.93*	*4.00*	*3.76*
Bwg for the entire gestational period (0 - 29) (in kg)	*0.65*	*0.54*	*0.52*	*0.55*	*0.37***

** $p < 0.01$

- *absolute and relative organ weight data for the parental animals :*
    - *Gravid uterine weight : significantly reduced at 45 mg/kg bw/d (0.56, 0.54, 0.51, 0.53, 0.46** kg respectively at 0, 5, 15, 30 and 45 mg/kg bw/d)*
- *number of female pregnant : 25, 24, 24, 25, 25 respectively at 0, 5, 15, 30 and 45 mg/kg bw/d*
- *duration of gestation : no effects*
- *number of implantations, corpora lutea, litter size, live births : no effects*

	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*
Corpora lutea	*9.8*	*9.8*	*9.9*	*10.2*	*9.8*
Implantations	*9.0*	*9.0*	*8.8*	*9.3*	*9.0*
Litter size	*8.7*	*8.6*	*8.3*	*8.8*	*8.3*
Live foetuses	*217*	*207*	*199*	*218*	*157*
Dead foetuses	*0*	*0*	*0*	*1*	*0*

- *number of pre- and post-implantation loss : no effects*
- *number of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses :*
    - *Only 1 dead foetus was observed at 30 mg/kg bw/d.*
    - *Resorption : 0.3, 0.4, 0.4, 0.5 and 0.7 respectively at 0, 5, 15, 30 and 45 mg/kg bw.*

Dose level (mg/kg bw/d)	*0*	*5*	*15*	*30*	*45*
Early resorption	*1*	*2*	*4*	*10*	*6*
Late resorption	*7*	*8*	*7*	*3*	*8*

    - *Percent of dead or resorbed conceptuses by litter : 3.1, 4.7, 4.8, 6.4 and 7.0 respectively at 0, 5, 15, 30 and 45 mg/kg bw/d*

For foetus/pups (per dose) :

- *mean number of live pups (litter size) : no effects*
- *sex ratio : no effects*
- *mean litter or pup weight by sex and with sexes combined : foetal body weight : significantly reduced at the highest dose*

	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 fetuse bw (in g)	*44.92*	*43.91*	*44.25*	*42.39*	*39.65***
Female fetuse bw (in g)	*42.92*	*42.79*	*43.64*	*42.20*	*38.70**

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

- *external, soft tissue and skeletal malformations and other relevant alterations : at the highest dose, a few alterations of the urogenital system were noted such as low set, small or absent kydneys and/or absent ureter*

	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*
Fetal incidence of low set of kidney	*0*	*0*	*0*	*0*	*3***
Fetal incidence of small kidneys	*0*	*0*	*0*	*0*	*3***
Fetal incidence of absent kidneys	*0*	*0*	*0*	*0*	*2***

** p < 0.01

3.10.1.6 A subacute toxicity study (28days) performed in mice

Study reference:

Wahle B.S., 2004a

Detailed study summary and results:

Test type

Following GLP regulation

Non guideline

Test substance

- *1,2,4-triazole*
- *Degree of purity : 99.9 %*
- *Batch number : S13691*

Test animals

- *Species/strain/sex : Mice / CD-1 [ICR]/BR / both sexes*
- *No. of animals per sex per dose : 15/sex/dose*
- *Age and weight at the study initiation : 8 weeks old*

Administration/exposure

- *route of administration : oral (feed)*
- *duration and frequency of exposure period : approximately 4 weeks, daily*
- *doses/concentration levels : 0, 50, 250, 500 and 2000 ppm. Corresponding to (in mg/kg bw/d) :*

	0 ppm	*50 ppm*	*250 ppm*	*500 ppm*	*2000 ppm*
♂	*0*	*9*	*47*	*90*	*356*
♀	*0*	*12*	*60*	*120*	*479*

- *post exposure observation period : no*

- *vehicle: ethanol*

Results and discussion

NOAEL (males) : 500 ppm

NOAEL (females) : 2000 ppm

- *mean body weight (in g) at day 28 of exposure : no effects observed*

	0 ppm	*50 ppm*	*250 ppm*	*500 ppm*	*2000 ppm*
♂	*35.4*	*35.9*	*35.5*	*35.6*	*33.8*
♀	*26.9*	*26.9*	*26.7*	*25.9*	*26.4*

- *food/water consumption : no effects observed*
- *description, severity, time of onset and duration of clinical signs : no effects observed*
- *haematological findings :*

  in males : significant decrease of Hgb in male at 250 and 2000 ppm (15.3 g/dl at 500 ppm and 15.3* g/dl at 2000 ppm vs 16.4 g/dl in control group) and statistically significant increase of HDW at 2000 ppm (1.99* vs 1.85 g/dl in control group)*

  In females : no effects observed
- *clinical biochemistry findings : no effects observed*
- *terminal body weight and absolute organ weight : no effects observed*
- *gross pathology findings : no effects observed*
- *histopathology findings : No statistically significant effects observed*

		0 ppm	*50 ppm*	*250 ppm*	*500 ppm*	*2000 ppm*
Epididymis	*Incidence of aspermia*	*0/15*	*0/15*	*0/15*	*1/15*	*0/15*
	Incidence of germ cells/debris	*0/15*	*1/15*	*1/15*	*0/15*	*3/15*
Testis	*Incidence of apoptotic-like bodies*	*2/15*	*4/15*	*1/15*	*3/15*	*5/15*
	Incidence of spermatid degeneration/depletion/asynchrony	*1/15*	*1/15*	*1/15*	*0/15*	*5/15*
	Incidence of tubular atrophy	*1/15*	*2/15*	*1/15*	*2/15*	*4/15*

- *mortality and time to death (if occurring) : 1 male in the lowest dose group (50 ppm) at day 23 of exposure, 1 female in control group at day 23 of exposure, 1 female in 500 ppm group at day 23 of exposure and 2 females in the highest dose group (2000 ppm) at day 24 of exposure.*

3.10.1.7 A subacute toxicity study (30 days) performed in rats

Study reference:

Anonymous (cited in US EPA memorandum, 2006)

Detailed study summary and results:

Test type

30-day oral toxicity study

Non-guideline

Test substance

- *1,2,4-triazole*
- *Degree of purity : no information available*

Test animals

- *Species/strain/sex : rats / no more information available*
- *No. of animals per sex per dose : no information available*
- *Age and weight at the study initiation : no information available*

Administration/exposure

- *route of administration : oral*
- *duration and frequency of test/exposure period : 30-day*
- *doses/concentration levels : 0, 8, 57 and 400 mg/kg bw/d*
- *vehicle: no information available*

Results and discussion

NOAEL : < 8 mg/kg bw/d

- *body weight and body weight changes : lower bw at the highest dose level (no more information available)*
- *food/water consumption : no information available*
- *description, severity, time of onset and duration of clinical signs : a few clinical signs were observed such as staggering, tremors and hunched posture however no more information available*
- *haematological findings : at 57 mg/kg bw/d, slight hematology changes were noted (no more information available)*
- *clinical biochemistry findings : no information available*
- *gross pathology findings : at 8 mg/kg bw/d, adrenal weight was reduced*
- *histopathology findings : no information available*
- *mortality and time to death : no information available*

3.10.1.8 A subchronic toxicity study (90 days) performed in rats

Study reference:

Bomhard E. et al., 1979

Detailed study summary and results:

Test type

Similar to OECD TG 408

Not following GLP regulation

Test substance

- *1,2,4-triazole*
- *Degree of purity : 99.6 %*

Test animals

- *Species/strain/sex : rat / Wistar / both sexes*
- *No. of animals per sex per dose : 15/sex/dose*
- *Age and weight at the study initiation : 5-6 weeks old and approximately 82 g for males and 78 g for females*

Administration/exposure

- *route of administration : oral (feed)*
- *duration and frequency of exposure period : 3 months, daily*
- *doses/concentration levels : 0, 100, 500 and 2500 ppm corresponding to (in mg/kg bw/d) :*

	0 ppm	*100 ppm*	*500 ppm*	*2500 ppm*
♂	*0*	*7.79*	*37.85*	*212.30*
♀	*0*	*10.23*	*54.20*	*266.69*

- *post exposure observation period : no*
- *vehicle: 90% pre-mix with ultrasil VN 3*

Results and discussion

NOAEL : 500 ppm

- *body weight and body weight changes : a statistically significant decrease was observed at the highest dose in both sexes*

  Initial and terminal bw (in grams)

Sex	*Study period*	*0 ppm*	*100 ppm*	*500 ppm*	*2500 ppm*
♂	*Initial bw*	*82*	*82*	*82*	*82*
	Terminal bw	*335*	*342*	*344*	*306***
♀	*Initial bw*	*78*	*78*	*78*	*78*
	Terminal bw	*195*	*195*	*187*	*184**

- *clinical signs : at the highest dose, 2 males and 2 females exhibited temporary slight convulsions*
- *haematological findings : a statistically significant lower haemoglobin, haematocrit, MCH and MCV were noted at the highest dose in males that pointed to slight anemia*
- *clinical biochemistry findings : no effects observed*
- *gross pathology findings : no effects observed*
- *organ weight : a statistically significant lower body weight was observed in both sexes at the highest dose (in males : 335, 342, 344 and 306* g respectively at 0, 100, 500 and 2500 ppm and in females :*

195, 195, 187 and 184 g respectively at 0, 100, 500 and 2500 ppm). At this dose a statistically significant testis weight decrease was also observed (3418, 3308, 3247 and 3215* mg respectively at 0, 100, 500 and 2500 ppm). Furthermore, in males, a few other organ weights were statistically modified such as a lower thymus weight, a lower heart weight, a lower lung weight (also observed in females) and a lower spleen weight.*

- *histopathology findings: no treatment-related findings*
- *mortality : no mortality observed*

3.10.1.9 A subchronic study (90 days) performed in mice

Study reference:

Wahle B.S., 2004b

Detailed study summary and results:

Test type

Following US EPA OPPTS 870.3100

Following GLP regulation

90 days toxicity study

Additional groups were performed and were sacrified after an exposure period of 28 days

Test substance

- *1,2,4-triazole*
- *Degree of purity : 99.9 %*
- *Batch number : S13691*

Test animals

- *Species/strain/sex : Mouse / CD-1[ICR]/BR / both sexes*
- *No. of animals per sex per dose : 20/sex/dose*

  + additional animals : 15/sex/group at 0, 3000 and 6000 ppm for an exposure period of 28 D and killed for hepatic enzyme analyses
- *Age and weight at the study initiation : 8 weeks old*

Administration/exposure

- *route of administration : oral (feed)*
- *duration and frequency of exposure period : 90 days, daily*
- *doses/concentration levels : 0, 500, 1000, 3000 and 6000 ppm, corresponding to (in mg/kg bw/d) :*

	0 ppm	*500 ppm*	*1000 ppm*	*3000 ppm*	*6000 ppm*
♂	*0*	*80*	*161*	*487*	*988*
♀	*0*	*105*	*215*	*663*	*1346*

- *post exposure observation period : no*

- *vehicle: ethanol*

Results and discussion

NOAEL (males) : 1000 ppm

NOAEL (females) : 3000 ppm

- *body weight and body weight changes : a significant body weight decrease was observed in males at 3000 and 6000 ppm (approximately -6 and -16 %) and in females at 6000 ppm (approximately -9 %).*

	BW at D84	*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**

** $p \leq 0.05$*

- *clinical signs: at the highest dose, an increase incidence of tremors was observed in both sexes (more marked in males). Furthermore, in males a statistically significantly increase of yellow staining and rough coat were observed at this dose level.*

  Incidence of tremors :

  In males : 0, 0, 0, 1 and 11 respectively at 0, 500, 1000, 3000 and 6000 ppm

  In females : 0, 0, 0, 2 and 2 respectively at 0, 500, 1000, 3000 and 6000 ppm

- *ophthalmologic findings: no information available*
- *haematological findings: a statistically significant decrease of Hgb and a statistically significant increase of RDW and HDW were observed at 6000 ppm in both sexes*
- *clinical biochemistry findings: a significant increase of cholesterol was observed at 3000 and 6000 ppm in females. In liver tissue, an increased activities of 7—ethoxycoumarin deethylase (ECOD), 7-ethoxyresorufin deethylase (EROD) and Aldrin epoxide (ALD) were observed in the additional group exposed during 28 D to 3000 and 6000 ppm and at the highest dose after 13 weeks of exposure.*
- *organ weight :*
  - *Absolute organ weight : terminal body weight and brain weight were statistically significantly decreased in both sexes at the highest dose. Moreover in males, testis weight was also statistically significantly reduced at this dose.*

At day 89		*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 weight (in g)	♂	*0.488*	*0.491*	*0.476*	*0.465**	*0.445**
	♀	*0.485*	*0.489*	*0.483*	*0.475*	*0.451**

Testis weight (in g)		*0.253*	*0.247*	*0.233*	*0.233*	*0.219**

** p ≤ 0.05*

- *Relative organ weight :*

At day 89		*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 weight (in %)	♂	*1.328*	*1.378*	*1.365*	*1.376*	*1.462**
	♀	*1.737*	*1.756*	*1.731*	*1.717*	*1.734*
Testis weight (in %)		*0.688*	*0.692*	*0.669*	*0.687*	*0.719*

** p ≤ 0.05*

- *histopathology findings: effects were observed in brain in both sexes. Furthermore, testis and epididymis were also affected.*

			0 ppm	*500 ppm*	*1000 ppm*	*3000 ppm*	*6000 ppm*
Brain	*Incidence of Purkinje cell loss*	♂	*0/20*	*0/20*	*0/20*	*0/20*	*15*/20*
		♀	*0/20*	*0/20*	*0/20*	*0/20*	*10*/20*
Epididymis	*Incidence of exfoliated germ cells/debris*		*0/20*	*0/20*	*0/20*	*0/20*	*10*/20*
Testis	*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)*

*() : average severity of animals with lesions : 1 (minimal) to 5 (severe); * p ≤ 0.05*

- *mortality : no effects observed*

3.10.1.10 A combined subchronic toxicity / neurotoxicity screening study performed in rats

Study reference:

Wahle B.S. and Sheets L.P., 2004

Detailed study summary and results:

Test type

Combined subchronic toxicity/neurotoxicity screening study

90-day

Following OECD TG 408 and 424

Animals were also tested for functional observational battery (FOB) and motor activity (12 males and 12 females /groups) : before the exposure and again during weeks 2,4,8 and 13 of exposure. At the study termination, 10 males and 10 females / groups were killed and perfused in situ for neuropathological examination.

Test substance

- *1,2,4-triazole*
- *Degree of purity : 99.9 %*
- *Batch number : S13691*

Test animals

- *Species/strain/sex : Rat / Wistar hanover / both sexes*
- *No. of animals per sex per dose : 20/sex/dose*
- *Age and weight at the study initiation : 8 weeks old*

Administration/exposure

- *route of administration : oral (feed)*
- *duration and frequency of exposure period : 90 days, daily*
- *doses/concentration levels : 0, 250, 500, 3000 and 1000/4000 ppm, corresponding to (in mg/kg bw/d) :*

	0 ppm	*250 ppm*	*500 ppm*	*3000 ppm*	*1000/4000 ppm*
♂	*0*	*16*	*33*	*183*	*210*
♀	*0*	*19*	*41*	*234*	*275*

The dose of 1000 ppm has been changed after 4 weeks of exposure in 4000 ppm for the rest of the study period. For 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.

- *post exposure observation period : no*
- *vehicle: ethanol*

Results and discussion

NOAEL : 500 ppm

- *body weight and body weight changes : a lower body weight was observed at 3000 and 1000/4000 ppm dose group. Body weight gain was also affected at these doses (approximately -18 % in ♂ and -19 % in ♀ at 3000 ppm and -21 % in both sexes at 1000/4000ppm).*

		0 ppm	*250 ppm*	*500 ppm*	*3000 ppm*	*1000/4000 ppm*
Bw (D0) (in	♂	265.6	267.4	267.0	267.1	266.1

g)	♀	181.2	181.4	180.7	179.9	182.7
BW (at 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**

* *p ≤ 0.05*

- *clinical signs : no effects observed*
- *Functional observational battery : effects were noted in both sexes at the 2 highest dose. These effects (tremors, gait incoordination, decreased rearing, ungroomed appearance, red nasal and lacrimal stain, muscle fasciculations, uncoordinated righting reflex) were more marked at 8 weeks than at 13 weeks of exposure. Increased incidence of foot splay was noted in males.*
- *motor activity assessment : no treatment-effects observed*
- *ophthalmologic findings : retinal degeneration was observed in 4 out of 20 males and in 2 out of 20 females at 3000 ppm, in 5 out of 20 males and in 5 out of 20 females at 1000/4000 ppm vs in 2 out of 20 males and in 0 out of 20 females in control group.*
- *haematological findings :*
    - *in males : at ≥ 500 ppm, astatistically significant decrease of haemoglobin and haematocrit were observed (Hgb : 16.0*, 15.7* and 15.8* g/dl respectively at 500, 1000/4000 and 3000 ppm vs 16.7 in control and Hct : 45.1*, 43.7* and 44.6* % respectively at 500, 1000/4000 and 3000 ppm).*
    - *In females : a statistically significant increase of platelets was observed at the 2 highest dose (911* and 903* 10*3/mm^3 respectively at 1000/4000 and 3000 ppm vs 785 10*3/mm^3 in control group). Moreover a statistically significant lower Hgb and MCV were noted at 3000 ppm (Hgb : 15.7* g/dl vs 16.3 and MCV 50.6* um³ vs 54.3 in control group).*
- *clinical biochemistry findings :*
    - *in males : statistically significant changes of CL, Trig, Calc, TSH were noted at the 2 highest doses*
    - *in females : statistically significant differences of K, CL and Calc at 3000 ppm and TSH at 1000/4000 ppm.*
- *Hepatic enzyme profile : at the 2 highest dose levels, a slightly increased activity for N-demethylase in males, O-demethylase in females and ECOD, EROD and ALD in both sexes.*
- *gross pathology findings : no effects observed*
- *organ weight (in g):*

		0 ppm	*250 ppm*	*500 ppm*	*1000/4000 ppm*	*3000 ppm*
♂	*Term.bw*	*432.6*	*428.1*	*427.6*	*385.8**	*402.8*

	Brain weight	*2.046*	*2.022*	*2.009*	*1.922**	*1.941**
	Testis weight	*3.732*	*3.660*	*3.651*	*3.621*	*3.619*
	Epidid. weight	*1.827*	*1.849*	*2.078*	*1.590*	*1.728*
♀	*Term.bw*	*239.1*	*242.5*	*234.3*	*230.9*	*226.6*
	Brain weight	*1.915*	*1.891*	*1.878*	*1.814*	*1.784**
	Ovary weight	*0.169*	*0.165*	*0.162*	*0.172*	*0.156*
	Uterus weight	*0.611*	*0.568*	*0.602*	*0.521*	*0.491*

* $p \leq 0.05$

No changes on relative organ weight observed on these organs.

- *histopathology findings : No effects observed on reproductive organs at the examined dose (0 and 1000/4000 ppm, the other dose levels were not tested). Only a slight increased number of corpora lutea at 3000 ppm and at 1000/4000 ppm levels (33, NE, 33, 41 and 40).*

  For the nervous system : degeneration of some nerve fibers were observed at the 2 highest doses. Moreover a degeneration/necrosis on the cerebellum (brain level 7) was noted at these 2 dose levels (in 9♂/10 tested and in 10♂/10 tested respectively at 1000/4000 and 3000 ppm and 10♀/10 tested at the 2 highest doses).
- *mortality : no effects observed*

3.10.1.11 A chronic toxicity study (12 months) performed in rats

Study reference:

Wahle B.S., 2010

Detailed study summary and results:

Test type

Following OECD TG 452

Folliwing GLP regulation

Test substance

- *1,2,4-triazole*
- *Degree of purity : ≥98.5 %*
- *Batch number : S4317788*

Test animals

- *Species/strain/sex : rat / Crl:Wi(Han) / both sexes*
- *No. of animals per sex per dose : 20 /sex/dose*

  + additional animals : 10/sex/group for neurotoxicology assessment
- *Age and weight at the study initiation : age : 8 w and weight : 133 – 255 g for males and 153 – 191 g for females*

Administration/exposure

- *route of administration : oral (feed)*
- *duration and frequency of test/exposure period : 12 months, daily*
- *doses/concentration levels : 0, 125, 375, 1000 and 2000 ppm corresponding to (in mg/kg bw/d):*

	0 ppm	*125 ppm*	*375 ppm*	*1000 ppm*	*2000 ppm*
Males	*0*	*6.9*	*21*	*58*	*113*
Females	*0*	*8.3*	*26*	*71*	*136*

- *post exposure observation period : no*
- *vehicle: ethanol*

Results and discussion

NOAEL : 375 ppm

- *body weight and body weight changes : lower bw and bwg at 1000 and 2000 ppm*

		0 ppm	*125 ppm*	*375 ppm*	*1000 ppm*	*2000 ppm*
BW at D 343	*Males*	*543*	*558*	*545*	*514*	*512*
	Females	*320*	*314*	*297*	*292*	*291*
BWG	*Males*	*318*	*332*	*321*	*293*	*294*
	Females	*144*	*139*	*123*	*116*	*115*

- *food/water consumption : no effects*
- *description, severity, time of onset and duration of clinical signs : no effects*
- *neurological assessments (functional observational battery and motor activity) : no statistically significant effects*
- *haematological findings: no effects*
- *clinical biochemistry findings: no effects*
- *gross pathology findings: no effects*
- *organ weight : no effects*
- *histopathology findings: statistically significant higher incidence of Purkinje cells loss within the vermis at the highest dose level*
- *mortality and time to death (if occurring) : no effects*
- *oestrous cycle : no effects*
    - *Number of oestrous cycle : 2.1, 1.4, 1.6, 2.3 and 1.6 respectively at 0, 125, 375, 1000 and 2000 ppm*
    - *Cycle length : 6.6, 5.1, 4.9*, 5.7 and 5.2 respectively at 0, 125, 375, 1000 and 2000 ppm*
- *sperm analyses : no effects*
    - *Mean % motility : 84.5, 83.5, 85.4, 86.1 and 82.3 respectively at 0, 125, 375, 1000 and 2000 ppm*

- *Mean % progressive : 58.5, 59.1, 62.1, 62.9 and 57.4 respectively at 0, 125, 375, 1000 and 2000 ppm*
- *Sperm count (sperm/g) : in testis : 37.2 at 2000 ppm vs 34.7 in control group*

  In epididymis : 103.7 at 2000 ppm vs 79.7 in control group
- *Sperm morphology : mean total number of normal sperm : 196.3 at 2000 ppm vs 197.9 in control group*

  mean total number of abnormal sperm : 3.0 at 2000 ppm vs 2.0 in control group

  mean total number of detached head : 0.7 at 2000 ppm vs 0.1 in control group

3.10.2 Human data

No information available

3.10.3 Other data (e.g. studies on mechanism of action)

No information available

3.11 Specific target organ toxicity – single exposure

Not evaluated in this dossier.

3.12 Specific target organ toxicity – repeated exposure

Not evaluated in this dossier.

3.13 Aspiration hazard

Not evaluated in this dossier.

4 ENVIRONMENTAL HAZARDS

Not evaluated in this dossier