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:

3-methylpyrazole

EC Number: 215-925-7

CAS Number: 1453-58-3

Index Number: NA

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1 PHYSICAL HAZARDS

Not evaluated in this CLH dossier.

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

2.1.1 Toxicokinetics *in vivo* study (anonymous 11 (1982))

Study reference:

Anonymous 11 (1982)

Test type

Non-guideline

Non-GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* no information available
- *Vehicle :* water

Test animals

- *Species/strain/sex :* rat / Wistar / both sexes
- *No. of animals per sex per dose :* 5/sex for ADE examination, 3/sex for M analysis and 3 animals to examine the passage of the placental barrier

Administration/exposure

- *Mode of administration* : gavage
- *Duration of test/exposure period :* single exposure, 5 or 7 times
- *Doses/concentration levels :* 5 mg/kg bw (for single and 5 times exposure) and 50 mg/kg bw (for 7 times exposure)
- *Control group and treatment :* /

Detailed study summary and results:

After administration, the maximal organ burden was determined after 30-60min. Quickly after, the substance is excreted via urine (93-96% within 24h. Moreover, 3-methylpyrazole crosses the placental barrier.

3 HEALTH HAZARDS

3.1 Acute toxicity - oral route

3.1.1 Animal data

3.1.1.1 Acute oral toxicity study (anonymous 12 (2012))

Study reference:

Anonymous 12 (2012)

Detailed study summary and results:

Test type

OECD guideline 423

GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* 97.9%

Test animals

- *Species/strain/sex :* rat / CD(Crl:CD(SD) / female
- *No. of animals per sex per dose :* 3 females/dose

Administration/exposure

- *Mode of administration* : gavage
- *Duration of test/exposure period :* single exposure
- *Doses/concentration levels :*
    - 3 females exposed to 2000 mg/kg bw. If 2/3 died -> testing to 300 mg/kg bw
    - 3 females exposed to 300 mg/kg bw. If 2/3 died -> testing to 50 mg/kg bw
    - 3 females exposed to 50 mg/kg bw. If 2/3 died -> testing to 5 mg/kg bw
    - 3 females exposed to 5 mg/kg bw.

  (If less than 2 animals died at 1 dose, the test item was retested)
- *Post exposure observation period :* 14d
- *Control group and treatment :* /
- *Vehicle :* 0.8% aqueous hydroxyl-methylcellulose

Results and reliability

- *LD50 or LC50 value :* > 300 - < 2000 mg/kg bw
- *Number of deaths at each dose level and time of death :*

  Table 1 : Mortality

Mortality	2000 mg/kg bw	300 mg/kg bw (first step)	300 mg/kg bw (second step)
Within 24h	2	0	0

Within 7d	3	0	0
Within 14d	3	0	0

- *Clinical signs:* animals exposed to 2000 mg/kg bw exhibited reduced motility and muscle tone, ataxia, dyspnoea and dorsal position. No effects were observed at 300 mg/kg bw.
- *Necropsy findings :* no effects observed

3.1.2 Human data

No information available

3.1.3 Other data

No information available

3.2 Acute toxicity - dermal route

No information available

3.3 Acute toxicity - inhalation route

3.3.1 Animal data

3.3.1.1 Acute inhalation toxicity study (anonymous 13 (1988))

Study reference:

Anonymous 13 (1988)

Detailed study summary and results:

Test type

Similar to OECD TG 403

No GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* no information available

Test animals

- *Species/strain/sex :* rat / Wistar / both sexes
- *No. of animals per sex per dose :* 5/sex/dose

Administration/exposure

- *Type of inhalation exposure and test conditions :* gas (no more information available)
- *Duration of test/exposure period :* 4h

- *Doses/concentration levels :* 2065, 3380, 4180, 7930, 18750 and 28110 mg/m³
- *Analytical verification of test atmosphere concentrations :* no

Results

- *LC50 :* > 28000 mg/m³
- *Mortality :* no animals died
- *Clinical signs :* no effects
- *Necrospy findings :* no effects

3.3.2 Human data

No information available

3.3.3 Other data

No information available

3.4 Skin corrosion/irritation

3.4.1 Animal data

No information available

3.4.2 Human data

No information available

3.4.3 Other data

3.4.3.1 *In vitro/ex vivo* eye irritation study (anonymous 14 (2011))

Study reference:

Anonymous 14 (2011)

Detailed study summary:

OECD TG 431, human skin model test (no deviations)

Test substance : 3-methylpyrazole (purity : 98.10%)

Conc. : 50 µl

Duration of exposure : 3 min and 1 h

Number of tissues : 2

Results :

After 3 min of exposure : relative absorbance value : 73.8 % (threshold for corrosivity : 50 %)

After 1 h of exposure : relative absorbance value : 14.9 % (threshold for corrosivity : 15 %)

Absorption value after 3min : 1.482 (negative control : 2.009; positive control : 0.586)

Absorption value after 1h : 0.281 (negative control : 1.883; positive control : 0.456)

3.5 Serious eye damage/eye irritation

3.5.1 Animal data

No information available

3.5.2 Human data

No information available

3.5.3 Other data

3.5.3.1 *In vitro/ex vivo* eye irritation study (anonymous 15 (2011))

Study reference:

Anonymous 15 (2011)

Detailed study summary:

BCOP test, bovine eye, OECD TG 437

3-methylpyrazole (purity : 98.10%)

Conc. : 750 µl

Duration of exposure : 10min

Results :

IVIS : 85.73 for test item (215.79 for positive control and -0.216 for negative control)

3.6 Respiratory sensitisation

No information available

3.7 Skin sensitisation

Not evaluated on this CLH report

3.8 Germ cell mutagenicity

Not evaluated on this CLH report

3.9 Carcinogenicity

Not evaluated on this CLH report

3.10 Reproductive toxicity

3.10.1 Animal data

3.10.1.1 Developmental toxicity study (anonymous 16 (1992))

Study reference:

Anonymous 16 (1992)

Detailed study summary and results:

Test type

OECD TG 414

GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* 99.9%

Test animals

- *Species/strain/sex :* rat / Wistar / pregnant females
- *No. of animals per sex per dose :* 25/group

Administration/exposure

- *Route of administration* : gavage
- *duration and frequency of test/exposure period :* GD 6-15
- *doses/concentration levels :* 0, 15, 45 and 90 mg/kg bw/d
- *vehicle :* water

Results and discussion

For dams :

- *time of death during the study and whether animals survived to termination :* no premature death observed
- *body weight data :* lower at the 2 highest dose levels.

Table 2 : Body weight data (in g)

Dose level (in mg/kg bw/d)	0	15	45	90
GD 0	225.0	222.4	223.7	224.9
GD 6	254.5	250.8	253.1	252.3
GD15	300.0	295.0	292.2	276.4**
GD20	373.3	368.4	364.2	352.6**
BWG GD 6-15	45.6	44.1	39.1	24.1**

BWG GD 0-20	148.3	146.0	140.4	127.7**
Gravid uterus weight	81.0	79.7	75.2	69.1**
Net weight change from D6	37.8	37.8	35.8	31.2*

* $p < 0.05$; ** : $p < 0.01$

- *clinical observations :* no effects
- *precoital interval (number of days until mating and number of estrous periods until mating)*
- *reproductive data :* unaffected (conception rate, mean number of corpora lutea, implantation sites, pre- and post-implantation loss, number of resorption and viable foetuses).
- *necropsy findings :* 1 female of the low dose exhibited hydrometra and did not become pregnant
- *gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight :* Uterus weight was significantly lower at the highest dose. Furthermore, the corrected bw (bw at GD20 minus uterus weight minus bw at GD6) was also significantly decreased at this dose level. (see table 2)

For foetuses :

- *mean number of live pups (litter size) :* mean number of live foetuses : 14.1, 14.0, 13.7 and 13.6 respectively at 0, 15, 45 and 90 mg/kg bw/d
- *placental weight :* no effects (0.45, 0.46, 0.46 and 0.43 g respectively at 0, 15, 45 and 90 mg/kg bw/d)
- *sex ratio :* no effects (51.5/48.5, 48.7/51.3, 50.1/49.9 and 47.2/52.8 % of live female/male respectively at 0, 15, 45 and 90 mg/kg bw/d)
- *mean litter or pup weight :* the mean fetal weight was significantly lower at the 2 highest dose levels (3.9, 3.8, 3.6** and 3.3**g respectively at 0, 15, 45 and 90 mg/kg bw/d).
- *fetal external malformations/variations :* one foetus of the 45 mg/kg bw/d level exhibited a cleft palate.
- *Fetal soft tissue malformations/variations :* Soft tissue examination revealed severe malformations in the urogenital tract and/or in the cardiovascular system in the foetuses of the highest dose.

Table 3 : Malformation data

Dose level (in mg/kg bw/d)	0	15	45	90
Fetal incidence	0	0	0	14**
Litter incidence	0	0	0	8**
Efferent urinary tract severely dilated	0	0	0	5*
Malformation of great vessels	0	0	0	6*
Agenesie of kidney(s)	0	0	0	2
Agenesie of ureter(s)	0	0	0	2
Dilatation of both ventricles (globular shaped heart)	0	0	0	2

* $p < 0.05$; ** : $p < 0.01$

- *Fetal skeletal malformations/variations :* Various malformation of the sternum and/or the vertebral column were also observed in all groups. For the control, the low and the mid dose groups, these malformation were within the range of the historical fetal incidence.

Table 4 : Skeletal malformations data

Dose level (in mg/kg bw/d)		0	15	45	90	Historical data in %
Nb. of foetuses evaluated (Nb. of litters evaluated)		174 (24)	159 (22)	177 (25)	176 (25)	
Fetal incidence		8	8	8	49**	
Litter incidence		6	6	5	20**	
Thoracic vertebral body/bodies dumbbell-shaped (%)	Fetal incidence (%)	6 (3.4)	5 (3.1)	3 (1.7)	39** (22)	0 – 8.8
	Litter incidence (%)	4 (17)	5 (23)	2 (8/)	17** (68)	0 – 39.1
Thoracic vertebral body/bodies bipartite (%)	Fetal incidence (%)	0	1 (0.6)	4 (2.3)	16** (9.1)	0 - 1.6
	Litter incidence (%)	0	1 (4.5)	2 (8.0)	10** (40)	0 – 9.5

* $p < 0.05$; ** : $p < 0.01$

3.10.1.2 Developmental toxicity study (Bleyl D.W.R., 1990)

Study reference:

Bleyl D.W.R. (1990)

Detailed study summary and results:

Test type

No guideline

No information about GLP compliance

The aim of this study was to reproduce the observation of urogenital syndrome after prenatal exposure.

Test substance

- 3-methylpyrazole
- *Degree of purity :* unknown

Test animals

- *Species/strain/sex :* rat / Wistar / female
- *No. of animals per sex per dose :* unknown

Administration/exposure

- *Route of administration* : oral (no more information)
- *duration and frequency of test/exposure period :* Pregnant rats were exposed only on GD 10 and GD 11
- *doses/concentration levels :* 0, 20, 40, 80 and 160 mg/kg bw/d
- *historical control data if available :* no information available
- *vehicle:* water

Description of test design:

- *details on mating procedure :* Mating, one male was left with two females for the night. Detection of sperm in the vaginal smear in the morning was monitored to determine the gestation day 1 (GD1). Fertilized females were then allocated to the different dose and control groups (6 dams per group).

Results and discussion

For dams:

- *body weight data for P :* no effects observed
- *clinical observations:* no information available
- *haematological and clinical biochemistry findings if available :* no information available
- *duration of gestation (calculated from day 0 of pregnancy) :* no information available
- *number of implantations, corpora lutea, litter size :* no information available
- *number of pre- and post-implantation loss :* no information available
- *number of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses :* no information available
- *necropsy findings :* no information available
- *histopathological findings: nature and severity :* no information available
- *body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight :* no information available
- *other organ weight changes* liver weight : no effects observed

For F1 pups/litters (per dose):

- *mean number of live pups (litter size) :* At the highest dose level, the rate of living pups at birth was of 77%**. No more information available
- *sex ratio :* no information available
- *viability index (pups surviving 4 days/total births) :* most animals exposed in utero to the highest dose died in the first days of life. No more information available
- *survival index at weaning :* 26%** at the highest dose. No more information available
- *mean litter or pup weight by sex and with sexes combined :* no information available
- *external, soft tissue and skeletal malformations and other relevant alterations :* 15.6% of the living fetuses of the 80 mg/kg bw/d dose level exhibited urogenital syndrome. In most cases, an unilateral kidney agenesis was noted (no left kidney) coupled with a hydronephrosis in the remaining kidney. The other pups exhibited a bilateral kidney agenesis. In males, the genital tract was complete however some cases of undescended testis were recorded. While in females, the kidney agenesis was always coupled with an incomplete differentiation of the uterus.

  The fetuses of the highest dose level died in the first day of live and the necropsy revealed urogenital syndrome.

- *data on physical landmarks in pups and other postnatal developmental data :* no information available
- *other information :* on PND 43 for males and PND 44 for females, the renal function of the surviving pups has been investigated and revealed disturbance only in females of the 2 highest dose levels.

Table 5 : Renal parameters data

Sex	Group	Dose (mg/kg)	Urine volume		Protein (g/L)	Creatinine (µmol/L)			Alk. Phosph.
			(mL)	(mL/kg)		Serum	Urine	Clearance (µL/sec)	
Male	0	0	3.7 ± 0.7	21.6 ± 3.9	0.48 ± 0.08	79.3 ± 2.9	2516 ± 524	2.57 ± 0.87	3.30 ± 20
	0_{HG}	0	4.5 ± 0.6	27.0 ± 3.3	0.36 ±0.05	76.2 ± 1.8	2340 ± 385	2.61 ± 0.62	269 ± 33
	2_{HG}	40	3.1 ± 0.4	18.1 ± 2.4	0.49 ± 0.05	74.9 ± 2.8	3420 ± 406	2.76 ± 0.48	249 ± 17
	3_{HG}	60	3.3 ± 0.5	19.6 ± 2.9	0.27 ± 0.04	77.0 ± 3.5	2092 ± 450	2.15 ± 0.85	217 ± 13
	4_{HG}	80	3.5 ± 0.4	21.2 ± 2.4	0.36 ± 0.06	79.6 ± 3.2	3140 ± 581	2.71 ± 0.68	216 ± 26
Female	0	0	2.7 ± 0.4	19.6 ± 2.9	0.23 ± 0.05	70.3 ± 3.7	3904 ± 241	2.03 ± 0.29	61 ± 11
	0_{HG}	0	2.5 ± 0.3	17.7 ± 2.0	0.24 ± 0.03	74.0 ± 3.1	3338 ± 634	2.22 ± 0.53	78 ± 13
	2_{HG}	40	2.2 ± 0.3	15.3 ± 2.2	0.21 ± 0.03	70.1 ± 3.0	2835 ± 752	1.77 ± 0.47	93 ± 23
	3_{HG}	60	2.3 ± 0.4	17.5 ± 3.3	0.23 ± 0.05	73.5 ± 3.7	3207 ± 646	1.96 ± 0.57	117 ± 55^{+}
	4_{HG}	80	1.6 ± 0.2^{+}	12.3 ± 1.2^{+}	0.33 ± 0.14^{+}	82.3 ± 5.6	1811 ± 500	0.67 ± $0.21^{\S}$	110 ± 31^{+}

$^{+}$ = p<0.05, § = p<0.01, $_{HG}$ = after addition of mercury

3.10.1.3 developmental toxicity study (Anonymous 17 (1984))

Study reference:

Anonymous 17 (1984)

Detailed study summary and results:

Test type

No guideline

No GLP compliance

Females were exposed to the test-substance on GD 4, 10, 13 and 18.

Test substance

- 3-methylpyrazole

- *Degree of purity :* not reported

Test animals

- *Species/strain/sex :* rat / Wistar / female
- *No. of animals per sex per dose :* 13, 13, 12, 14 and 6 female rats respectively at 0, 50, 100, 200 and 400 mg/kg bw/exposure

Administration/exposure

- *Route of administration :* gavage
- *duration and frequency of test/exposure period :* GD 4, 10, 13 and 18
- *doses/concentration levels :* 0, 50, 100, 200 and 400 mg/kg bw/exposure
- *vehicle:* water

Description of test design:

- For the mating, one male was left with two females for the night. Detection of sperm in the vaginal smear in the morning was monitored to determine the gestation day 1 (GD1). Fertilized females were then allocated to the different doses and control groups. Doses were given orally by gavage on GD4, GD10, GD13 and GD18. The test substance has been diluted in water, and the animals received 2.5 mL/kg bw. Body weight has been monitored on GD1, GD4, GD10, GD13, GD18 and GD20.The dams were killed by decapitation on GD20. After sacrifice, the liver has been weighted (absolute and relative).The numbers of corpora lutea, implantation, resorptions, live and dead fetuses have been recorded.
- Each living fetus was weighed, measured (crown-rump length) and examined to detect unexpected malformation. They were then fixed alternatively in a solution 96% ethanol (for skeletal examination) or in Bouin's solution (for soft tissue examination).

Results and discussion

For dams (per dose):

- *time of death during the study and whether animals survived to termination :* at the highest dose, 4 pregnant dams died (necropsy revealed a catarrhal enteritis and/or nephrosis)
- *body weight data for P animals :* significantly reduced at the highest dose level. The body weight of the 200 mg/kg bw/exposure dose level tend also to decline on GD20.

Table 6 : Body weight in g

Dose (mg/kg)	Body weight (g)					
	GD1	GD4	GD10	GD13	GD18	GD20
0	268 ± 8	276 ± 7	288 ± 8	298 ± 9	387 ± 9	334 ± 9
50	245 ± 7	257 ± 8	273 ± 9	279 ± 10	309 ± 18	328 ± 11
100	255 ± 7	262 ± 7	280 ± 8	283 ± 10	315 ± 7	292 ± 33
200	251 ± 5	260 ± 6	270 ± 6	275 ± 7	298 ± 7	306 ± 8^{+}
400	253 ± 15	264 ± 15	263 ± 15	256 ± 16§	246 ± 15§	258 ± 15§

$^{+}$ = $p<0.05$, §= $p<0.01$

- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :* liver weight was recorded and did not reveal modification (absolute liver weight : 12.2, 12.5, 13.1, 12.1 and 11.3g respectively at 0, 50, 100, 200 and 400 mg/kg bw/exposure; relative liver weight : 2.6, 3.8, 3.9, 4.0 and 4.2 g/100g bw respectively at 0, 50, 100, 200 and 400 mg/kg bw/exposure). No more information available
- *clinical observations:* no information available
- *haematological and clinical biochemistry findings if available :* no information available
- *duration of gestation (calculated from day 0 of pregnancy) :* no information available
- *number of implantation, corpora lutea, pre- and post-implantation loss :* no effects on the pre-implantation loss. Nevertheless, the post-implantation loss was significantly reduced at the highest dose level.

Table 7 : Reproductive parameters

Dose (mg/kg)	Corpora lutea	Implantations	Preimplantation losses	
			Absolute	Relative (%)
0	13.1 ± 0.5	12.0 ± 0.6	1.2 ± 0.3	8.9 ± 2.2
50	11.9 ± 0.7	10.5 ± 0.9	1.4 ± 0.5	11.3 ± 4.9
100	18.7 ± 0.4	11.5 ± 0.6	1.2 ± 0.4	9.2 ± 3.5
200	18.8 ± .5	11.6 ± 0.7	1.3 ± 0.4	10.1 ± 3.8
400	10.3 ± 1.7^{+}	9.7 ± 1.5	0.7 ± 0.3	5.1 ± 2.4

$^{+}$ = p<0.05

- *number of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses :* in 4 out of 6 dams of the highest dose, all the progeny died by resorption.

Table 8 : Resorption and post implantation losses

Dose (mg/kg)	Resorption (%)			Dead fetuses (%)	Total postimplantation losses	
	Early	Middle	Late		Absolute	Relat. (%)
0	9.6 ± 3.8	1.9 ± 1.4	0	0	1.5 ± 0.5	11.5 ± 3.7
50	6.7 ± 2.5	7.1 ± 3.2	0	0	1.2 ± 0.3	13.8 ± 3.7
100	10.1 ± 2.6	0	0	0	1.2 ± 0.4	11.8 ± 3.3
200	10.5 ± 2.4	3.0 ± 1.1	0.5 ± 0.5	0.5 ± 0.5	1.7 ± 0.4	14.9 ± 3.8
400	2.5 ± 2.5	69.8 ± 19.1§	0	2.6 ± 2.6^{+}	7.0 ± 1.9§	74.9 ± 16.2§

§= p<0.01

Table 9 : Total losses

Dose (mg/kg)	Total loss	
	Absolute	Relative (%)
0	2.6 ± 0.6	19.6 ± 3.7
50	2.5 ± 0.6	23.5 ± 6.5
100	2.4 ± 0.6	19.2 ± 5.3

200	3.0 ± 0.6	23.0 ± 4.9
400	7.5 ± 1.8§	77.8 ± 14.5§

§= p<0.01

- *necropsy findings :* no information available
- *histopathological findings: nature and severity :* no information available
- *body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight :* no information available

For F1 (per dose):

- *mean number of live pups (litter size) :* see table 10
- *sex ratio :* no information available
- *viability index (pups surviving 4 days/total births) :* no information available
- *survival index at weaning :* no information available
- *mean litter or pup weight by sex and with sexes combined :* the weight of living fetuses was significantly decreased. The placental weight was severely reduced at this dose level.

Table 10 : Body weight and placental weight of the living fetuses

Dose (mg/kg)	Live fetuses			Weight of placenta (g)
	Total	Length (mm)	BW (g)	
0	10.5 ± 0.6	30.9 ± 0.3	1.80 ± 0.04	0.43 ± 0.02
50	9.3 ± 1.0	30.2 ± 0.2	1.80 ± 0.02	0.46 ± 0.05
100	10.2 ± 0.8	29.3 ± 0.5	1.70 ± 0.05	0.46 ± 0.03
200	9.9 ± 0.7	27.2 ± 0.7+	1.40 ± 0.05§	0.41 ± 0.03
400	8.7 ± 1.7§	23.7 ± 1.8§	1.05 ± 0.07§	0.28 ± 0.04§

+ = p<0.05, §= p<0.01

- *external, soft tissue and skeletal malformations and other relevant alterations :* all the fetuses of the highest dose presented at least one malformation (46.8% at 200 mg/kg bw/exposure and 11.1% at 100 mg/kg bw/exposure).

Table 11 : Malformation data

Dose (mg/kg)	0	50	100	200	400
Syndactilie/Retrodactilie					
Total	0	0	1.2 ± 0.8	15.3 ± 6.3§	81.3 ± 18.8§
Forelimb	0	0	1.2 ± 0.8	14.0 ± 6.5§	81.3 ± 18.8§
Hind limb	0	0	0	4.6 ± 3.4	50.0 ± 37.5§
Amelia	0	0	0	1.2 ± 0.8	6.3 ± 6.3
Anemia	0	0	0	2.6 ± 1.5+	0
Cleft palate	0	0	0	0.5 ± 0.5	12.5 ± 12.5
Urogenital syndrome					
Total	0	0	4.4 ± 4.4	40.8 ± 8.0§	58.8 ± 31.3§

Symmetric	0	0	3.3 ± 3.3	27.6 ± 8.5§	50.4 ± 25.0§
Asymmetric	0	0	1.1 ± 1.1	13.2 ± 3.0	31.3 ± 6.3§
Hydronephrose	0.5 ± 0.5	2.0 ± 1.0	5.1 ± 2.4+	1.9 ± 1.0	0
Ecchymosis	0.5 ± 0.5	0	3.8 ± 2.6	1.2 ± 0.8	0
Horizonal cardiac apex	0	0	2.8 ± 1.5	4.2 ± 1.9	6.3 ± 6.3
Total (%)	0.5 ± 0.5	2.0 ± 1.0	11.1 ± 4.5	46.8 ± 6.8§	100 ± 0.1§

+ = p<0.05, § = p<0.01

3.10.1.4 Developmental toxicity study (anonymous 18 (1989))

Study reference:

Anonymous 18, 1989

Detailed study summary and results:

Test type

No guideline followed

No GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* no information available

Test animals

- *Species/strain/sex :* rat / strain unknown / female
- *No. of animals per sex per dose :* 8 pregnant females / group

Administration/exposure

- *Route of administration :* gavage
- *duration and frequency of test/exposure period :* GD6-18
- *doses/concentration levels :* 0, 25, 100, 175 and 225 mg/kg bw/d
- *historical control data if available :* no information available
- *vehicle:* no information available

Description of test design:

- *details on mating procedure :* no information available
- *post exposure observation period :* sacrificed on GD20

Results and discussion

For dams (per dose):

- *time of death during the study and whether animals survived to termination :* 6 females exposed to 175 mg/kg bw/d and all females exposed to 225 mg/kg bw/d died or were sacrificed in extremis.
- *body weight data for P :* moderate to severe decrease was noted during GD 6 to 12 in animals exposed to 100 mg/kg bw/d.

- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :* no information available
- *clinical observations: :* no information available
- *haematological and clinical biochemistry findings if available :* no information available
- *number of implantations, corpora lutea, litter size :* no information available
- *number of pre- and post-implantation loss :* no information available
- *number of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses :* an increase in resorptions was noted at 100 mg/kg bw/d. no fetuses were produced by the 2 survivor females exposed to 175 mg/kg bw/d.
- *number of live births :* no information available
- *necropsy findings :* no information available
- *histopathological findings: nature and severity :* no information available
- *body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight :* no information available
- *other organ weight changes if available :* no information available

For F1 pups/litters (per dose):

- *mean number of live pups (litter size) :* no information available
- *sex ratio :* no information available
- *viability index (pups surviving 4 days/total births) :* no information available
- *survival index at weaning :* no information available
- *mean litter or pup weight by sex and with sexes combined :* fetal weight was reduced at 100 mg/kg bw/d.
- *external, soft tissue and skeletal malformations and other relevant alterations:* One fetus in the 100 mg/kg bw/d dose level exhibited external malformations such as cleft palate. However this foetus weighted only 1.2g.

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 CLH report

3.12 Specific target organ toxicity – repeated exposure

3.12.1 Animal data

3.12.1.1 Short-term oral toxicity study (anonymous 19 (1996))

Study reference:

Anonymous 19 (1996)

Detailed study summary and results:

Test type

OECD TG 407

GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* 99.7%

Test animals

- *Species/strain/sex :* mouse / B6C3F1 / both sexes
- *No. of animals per sex per dose :* 5/sex/dose

Administration/exposure

- *route of administration :* via drinking water
- *duration and frequency of test/exposure period :* 28d
- *doses/concentration levels :* 0, 900, 1125 and 1575 ppm (corresponding to a mean daily test substance intake of 0, 154, 176 and 206 mg/kg bw/d respectively)

Results and discussion

- *body weight and body weight changes :* Body weight was unaffected in all dose levels (29.3/23.7, 28.6/23.7, 28.0/23.7 and 28.7/22.9g in males/females respectively at 0, 900, 1125 and 1575 ppm), however body weight gain was significantly lower in females of the highest dose level (BWG 0-28D : 4.3/4.6, 3.5/4.1, 3.0/4.2 and 3.8/3.4** g in males/females respectively at 0, 900, 1125 and 1575 ppm).
- *description, severity, time of onset and duration of clinical signs :* no effects observed
- *gross pathology findings:* Necropsy revealed a significant higher lung weight in both sexes at the highest dose level and in males at the lowest dose level. Liver weight was significantly reduced at 1125 ppm in male. The relative organ weight observation showed only changes in lung.
- *histopathology findings:* Histopathology examination was only performed on the lungs. Lesions of the mucus cells of the air ducts and of the Clara cells in the bronchi and bronchioles were recorded. Clara cells alteration consisted of disorganization of the luminal lining cell layer due to flattening of the cells and loss of the apical parts of the Clara cells and due to development of irregular shape

shaped clara cell nuclei. Moreover, hypotrophy of the air duct epithelia (focal or diffuse) was recorded

- *mortality and time to death :* no effects observed

3.12.1.2 Short-term oral toxicity study (anonymous 20 (1997))

Study reference:

Anonymous 20 (1997)

Detailed study summary and results:

Test type

EU Method B.7

GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* 99.4%

Test animals

- *Species/strain/sex :* mouse / B6C3F1 / both sexes
- *No. of animals per sex per dose :* 5/sex/group for main groups + 5/sex/group for recovery groups

Administration/exposure

- *route of administration :* via drinking water
- *duration and frequency of test/exposure period :* 28d
- *doses/concentration levels :* 300, 900 and 1575 ppm (corresponding to 0/0, 70/82, 151/193 or 223/252 mg/kg bw/d respectively in males/females)
- *post exposure observation period :* 14d for recovery groups

Results and discussion

- *body weight and body weight changes :* The body weight examination revealed a statistically significant lower value in females at the highest dose. The body weight gain was already decreased in females at 900 ppm and in males at 1575 ppm. However, during the recovery period, no differences in body weight were observed.
- *description, severity, time of onset and duration of clinical signs :* Females of the mid and high dose level exhibited tremors and/or hunched posture.
- *gross pathology findings:* Macroscopic observations did not reveal any treatment-related changes.
- *organ weight :* The absolute lung weight was increased in females at the mid and high dose level, whereas the relative lung weight was already increased in females at the low dose level and was also increased in males at the mid and high dose level. Whereas, the necropsy of animals of the recovery groups revealed that the absolute lung weight was increased in females at the mid dose level while the relative lung weight was increased in females at 900 and 1575 ppm.

- *histopathology findings :* The microscopic examination of the main groups revealed a Clara cell alteration (moderate at 300 and 900 ppm, and moderate to marked at 1575 ppm). This modification was characterized by a loss of the characteristic dome-shaped appearance and the apical "bled", by cytokaryomegaly, and basophilia. Furthermore, at 1575 ppm, mitotic figures and/or macrophages were noted in the altered epithelium of the bronchi and bronchioli. In a few mice of the mid and high dose levels, interstitial histiocytosis, alveolar macrophages, alveolar hemorrhage, alveolar edema and/or interstitial edema/congestion were observed. The animals of all recovery groups showed also a Clara cell alteration (slight to moderate at 300 and 900 ppm and moderate to marked at 1575 ppm). In addition, slight to moderate Clara cell proliferation (characterized by increased numbers cytokaryomegalic, basophilic and sometimes multinuclear cells) was observed in all treated mice of these groups. These cells were arranged in two cell layers instead of the normal one layer. In addition, mitotic figures were occasionally observed.
- *mortality and time to death :* no effects observed

3.12.1.3 Short-term oral toxicity study (anonymous 21 (1996))

Study reference:

Anonymous 21 (1996)

Detailed study summary and results:

Test type

No guideline followed

No GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* 99.77%

Test animals

- *Species/strain/sex :* Mouse / B6C3F1 / both sexes
- *No. of animals per sex per dose :* 3/sex/dose

Administration/exposure

- *route of administration :* via drinking water
- *duration and frequency of test/exposure period :* 2w
- *doses/concentration levels :* 0, 225 and 675 ppm (corresponding to a test substance intake of 0/0, 47/61 and 140/173 mg/kg bw/d respectively in males/females)

Results and discussion

- *body weight and body weight changes :* Body weight examination did not reveal significant changes (at D14 : 25.0/21.0, 25.2/21.2 and 25.7/21.3 g respectively at 0, 225 and 675 ppm).
- *description, severity, time of onset and duration of clinical signs :* no effects observed

- *gross pathology findings:* Erosions/ulcers in the glandular stomach and discoloration of contents of the jejunum were observed in control and in dose groups (in 0/2 , 0/2 and 3 males/3females respectively at 0, 225 and 675 ppm).
- *mortality and time to death :* no effects observed
-

3.12.1.4 Subchronic oral toxicity study (anonymous 22 (1999))

Study reference:

Anonymous 22 (1999)

Detailed study summary and results:

Test type

OECD TG 407 and 408

GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* 99.34%

Test animals

- *Species/strain/sex :* rat / Wistar / both sexes
- *No. of animals per sex per dose :* 10/sex/group for main groups + 10/sex/group for recovery groups

Administration/exposure

- *route of administration :* via drinking water
- *duration and frequency of test/exposure period :* 90d
- *doses/concentration levels :* 0 and 40 mg/kg bw/d
- *post exposure observation period :* 28d for recovery groups

Results and discussion

- *body weight and body weight changes :* no effects observed
- *description, severity, time of onset and duration of clinical signs* : no effects observed
- *gross pathology findings:* the organ weight and histopathological examination were only performed on kidneys, liver and lungs. Significant higher absolute and relative kidney weight was noted in females (slight trend in males). Moreover, significant increase of liver weight (abs. and rela.) was observed in females. These changes did not appear at the end of the recovery period.

Table 12 : Organ weight

		Main groups				Recovery groups			
		Males		Females		Males		Females	
Dose level (mg/kg bw/d)		0	40	0	40	0	40	0	40
Kidney (left)	Abs	1572.0	1602.8	1046.9	1166.3*	1679.5	1628.1	1088.3	1025.5

weight (in mg)	Rela	0.3174	0.3356	0.3591	0.4006*	0.3294	0.3177	0.3420	0.3445
Kidney (right) weight (in mg)	Abs	1562.8	1595.3	1046.7	1183.8*	1653.6	1622.5	1067.7	1021.7
	Rela	0.3150	0.3347	0.3588	0.4069*	0.3239	0.3154	0.3349	0.3432
Liver weight (in mg)	Abs	20229.8	19642.3	11151.3	12594.8*	20788.0	18629.9	11149.9	9715.6*
	Rela	4.080	4.107	3.799	4.293*	4.036	3.596	3.474	3.271
Lungs weight (in mg)	Abs	2369.1	2241.0	1763.6	1865.4	2294.0	2234.1	1763.8	1731.7
	rela	0.4817	0.4692	0.6011	0.6381	0.4492	0.4346	0.5556	0.5823

- *histopathology findings:* 2 males of the control group and 1 male exposed to 40 mg/kg bw/d showed intracellular vacuoles in hepatocytes (low grade).
- *mortality and time to death :* no effects observed

3.12.1.5 Subchronic oral toxicity study (anonymous 23 (1980))

Study reference:

Anonymous 23 (1980)

Detailed study summary and results:

Test type

No guideline followed

No GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* no information available

Test animals

- *Species/strain/sex :* rat / Wistar / both sexes
- *No. of animals per sex per dose :* 24/sex/group (except for control group : 36/sex)

Administration/exposure

- *route of administration :* via gavage
- *duration and frequency of test/exposure period :* 90d
- *doses/concentration levels :* 0, 0.2, 2, 20 and 200 mg/kg bw/d

Results and discussion

- *body weight and body weight changes :* the body weight decreased at the highest dose level, the modification was more severe in males.

Table 13 : Body weight data

	Males					Females				
Dose level (in mg/kg bw/d)	0	0.2	2	20	200	0	0.2	2	20	200
W0	78	78	76	76	76	72	73	72	72	71

W6	270	283	276	274	198	201	200	202	200	168
W12	359	372	362	359	262	249	248	249	246	222

- *clinical biochemistry findings:* changes were noted during enzyme activity examination. At the highest dose level, aspartate aminotransferase, leucine aminotransferase and alkaline phosphatase activity were increased. Cholinesterase activity was reduced only in females at the highest dose level. (See table 14)

Table 14 : Enzyme activity data after 12w

Dose level (mg/kg bw/d)	Males					Females				
	0	0.2	2	20	200	0	0.2	2	20	200
Aspartate aminotransferase activity	1.54	1.31	1.43	1.45	2.02	1.44	1.45	1.51	1.31	1.79
Leucine aminopeptidase activity	6.25	5.36	6.15	6.38	8.60	6.12	6.80	6.70	6.81	10.57
Alkaline phosphatase activity	0.94	1.20	1.07	1.20	1.92	0.94	0.93	1.07	1.26	1.49
Cholinesterase activity	0.46	0.43	0.45	0.42	0.45	1.20	1.03	1.25	1.17	0.59

- *organ weight :* at necropsy, organ weight was examined and revealed some changes. Lower brain, spleen, thymus and testes weights were observed at the highest dose level compared to the control group. Liver weight was increased at 200 mg/kg bw/d compared to the control group.

Table 15 : Organ weight (in g and in %)

Dose level (in mg/kg bw/d)		Males					Females				
		0	0.2	2	20	200	0	0.2	2	20	200
Adrenal glands	Abs	0.063	0.071	0.072	0.072	0.065	0.066	0.068	0.075	0.069	0.068
	Rela	0.0179	0.0196	0.0205	0.0198	0.0271	0.0272	0.0281	0.0313	0.0294	0.0354
Brain	Abs	1.82	1.79	1.88	1.80	1.63	1.71	0.69	1.72	1.73	1.56
	Rela	0.516	0.495	0.537	0.496	0.673	0.704	0.703	0.720	0.735	0.822
Kidneys	Abs	2.80	2.91	2.93	2.93	2.48	1.97	2.06	2.04	1.86	2.14
	Rela	0.788	0.808	0.836	0.807	0.998	0.812	0.852	0.851	0.792	1.107
Liver	Abs	15.8	15.6	18.2	18.4	16.9	10.3	11.7	13.0	11.2	13.9
	Rela	4.43	4.31	5.19	5.02	6.76	4.23	4.79	5.42	4.74	7.22
Spleen	Abs	0.763	0.766	0.811	0.771	0.500	0.638	0.642	0.663	0.600	0.477
	Rela	0.215	0.212	0.231	0.212	0.198	0.262	0.264	0.276	0.254	0.248
Thymus	Abs	0.329	0.351	0.288	0.301	0.193	0.284	0.255	0.278	0.274	0.179
	Rela	0.093	0.097	0.082	0.081	0.070	0.117	0.105	0.115	0.117	0.093
Testes/ovary	Abs	3.03	3.07	3.04	3.13	2.17	0.106	0.108	0.106	0.121	0.097

	rela	0.84	0.85	0.86	0.86	0.86	0.0436	0.0444	0.0441	0.0514	0.0502

- *histopathology findings:*
    - Heart : no inflammatory or degenerative change has been observed. A slight activation of the histiocytes has been occasionally seen but was not treatment-related. Moreover one rat exposed to the highest dose developed a non-ulcerous epicardite (incidental findings).
    - Trachea/thyroid : cross-sections at the thyroid height revealed an intact ciliated epithelium, rarely artificially separated from its underlay. The glands found in the submucosa were surrounded by lymph tissue more or less dense, which is partly characteristic of lymph nodes. In some cases single excretory ducts were dilated and filled with granulocytes and cellular debris. Few animals (independently of the dose given) showed some chronic peritubular inflammation in the form of development of callous-fibrocytic sleeves.
    - Lungs : sections of the lungs revealed frequently massive clubbing of lymphocytes and to a lesser extent of histiocytes. But these were only rarely indicative of an inflammatory response. These effects were not treatment-related. One rat exposed to the highest dose showed a subacute ulcerous bronchitis and peribronchitis. Moreover one rat of the lowest dose group developed an ulcerous pneumonia in one lobules.
    - Thyroid : alteration thyroid gland (no more information available)
    - Liver : nucleus anisomorphism, fatty degeneration and cell death (no more information available)
- *mortality and time to death:* 2 males died during study (1 exposed to 20 mg and 1 exposed to 200 mg/kg bw/d).

3.12.1.6 Subchronic oral toxicity study (anonymous 24 (2000))

Study reference:

Anonymous 24 (2000)

Detailed study summary and results:

Test type

OECD TG 408

GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* 98.38%

Test animals

- *Species/strain/sex :* Mouse / B6C3F1 / both sexes
- *No. of animals per sex per dose :* 10/sex/group for main groups + 10/sex/group for recovery groups

Administration/exposure

- *route of administration :* via drinking water
- *duration and frequency of test/exposure period :* 13w
- *doses/concentration levels :* 0, 5, 10, 20 and 40 mg/kg bw/d
- *post exposure observation period :* 4w for observation groups

Results and discussion

- *body weight and body weight changes :* significant body weight changes were noted in males.

Table 16 : Body weight data

	Males					Females				
Dose level (in mg/kg bw/d)	0	5	10	20	40	0	5	10	20	40
No. animals examined	20	20	20	20	20	20	20	20	20	20
D1	24.3	23.4*	24.1	23.4*	23.4*	20.3	20.0	20.1	20.0	20.4
D40	30.3	28.4**	28.9*	28.3**	27.9**	24.9	24.7	24.5	24.4	24.8
D89	33.3	30.2**	30.8**	30.5**	29.5**	26.7	26.1	26.9	26.4	26.5
Recovery groups										
No. animals examined	10	10	10	10	10	10	10	10	10	10
D5	32.9	29.8*	30.9	31.0	29.2**	26.1	26.8	26.5	26.4	26.7
D26	35.0	32.5	34.1	33.6	31.4*	27.2	27.2	27.4	27.4	27.6

* : p < 0.05 ; ** : p < 0.01

- *description, severity, time of onset and duration of clinical signs :* no effects observed
- *gross pathology findings:* significant organ weight modifications were observed. Lung weight was not recorded.

Table 17 : Organ weight (in g or %)

		Males					Females				
Dose level (in mg/kg bw/d)		0	5	10	20	40	0	5	10	20	40
After 13w											
FBW		30.0	25.4**	24.6**	24.9**	25.0**	26.1	25.6	25.4	24.6	25.1
Adrenal glands	Abs	0.008	0.007	0.008	0.007	0.008	0.014	0.015	0.012	0.014	0.015
	Rela	0.026	0.028	0.031	0.030	0.031	0.053	0.058	0.049	0.056	0.060
Brain	Abs	0.488	0.483	0.494	0.483	0.486	0.488	0.501	0.495	0.496	0.500
	Rela	1.643	1.912**	2.017**	1.969**	1.948**	1.872	1.964	1.965	2.018*	2.000
Liver	Abs	1.25	1.08	1.13	1.11	1.17	1.63	1.59	1.48	1.51	1.62
	Rela	4.15	4.27	4.59**	4.48	4.68**	6.23	6.22	5.85	6.14	6.48
Spleen	Abs	0.069	0.056	0.059	0.051**	0.065	0.082	0.084	0.083	0.083	0.081
	Rela	0.229	0.223	0.240	0.204	0.260	0.315	0.329	0.328	0.336	0.323

Testes	Abs	0.235	0.234	0.232	0.235	0.232					
	Rela	0.792	0.927**	0.947**	0.954**	0.928**					
Thymus	Abs	0.035	0.030	0.024**	0.025**	0.029	0.027	0.029	0.025	0.025	0.023
	Rela	0.117	0.116	0.099	0.100	0.115	0.104	0.114	0.098	0.100	0.091

* : p < 0.05 ; ** : p < 0.01

- *histopathology findings:* the histopathological examination revealed changes in lungs such as an increase incidence of Clara cell alteration and proliferation.

Table 18 : Clara cells modifications

		Males					Females				
Dose level (in mg/kg bw/d)		0	5	10	20	40	0	5	10	20	40
After 13w											
Clara cell alteration	incidence	0	0	7	10	10	0	0	4	10	10
	Grade 1			3	2				1		
	Grade 2			4	7				2	6	
	Grade 3				1	5			1	4	3
	Grade 4					5					7
After 17w											
Clara cell alteration	Incidence	0	0	2	9	10	0	0	4	10	10
	Grade 1			1					1	1	
	Grade 2			1	7	1			3	9	
	Grade 3				2	9					10
Clara cell proliferation	Incidence	0	0	2	10	10	0	0	4	9	10
	Grade 1			2	2	3			3	2	1
	Grade 2				7	5			1	6	7
	Grade 3				1	2				1	2

- *mortality and time to death :* no effects observed

3.12.1.7 Chronic oral toxicity study (anonymous 25 (1985))

Study reference:

Anonymous 25 (1985)

Detailed study summary and results:

Test type

No guideline followed

No GLP

Test substance

- 3-methylpyrazole
- *Degree of purity :* no information available

Test animals

- *Species/strain/sex :* rat / Wistar / both sexes
- *No. of animals per sex per dose :* 32/sex/group

Administration/exposure

- *route of administration :* via drinking water
- *duration and frequency of test/exposure period :* 18m
- *doses/concentration levels :* 0, 10, 40 and 2000/1000 ppm (2000 ppm during w 1-4 thereafter 1000ppm during w 5-80)
- *vehicle:*

Results and discussion

- *body weight and body weight changes :* lower bw was observed at the highest dose

Table 19 : mortality and body weight (in g) observation

Dose level (in ppm)		0		10		40		40		2000/1000	
		Number of animals examined	bw	Number of animals examined	bw	Number of animals examined	bw	Number of animals examined	bw	Number of animals examined	bw
♂	W0	32	88	32	78	32	85	32	77	32	84
	W4	32	264	32	261	32	266	32	262	27	121
	W40	31	530	32	511	32	508	32	513	26	434
	W60	22	605	23	583	23	580	22	601	14	499
	W80	19	500	13	544	21	547	17	516	8	416
♀	W0	32	77	32	77	32	75	32	77	32	74
	W4	32	188	32	195	32	199	32	193	22	103
	W40	32	342	31	333	32	333	32	335	21	268
	W60	23	379	22	380	24	386	24	374	9	299
	W80	19	385	16	372	22	369	17	343	4	272

- *description, severity, time of onset and duration of clinical signs:* dyspnea, cachexia and pneumonia were observed in all dose levels.
- *haematological and clinical biochemistry findings:* hematological and bioclinical examination revealed changes at the highest dose level (see table 20).

Table 20 : Hematology and enzyme activity after 18 months

	Males					Females				
Dose level (in ppm)	0	10	40	40	2000/1000	0	10	40	40	2000/1000
Hb	167.5	168.7	162.9	156.5	155.1	149.0	147.1	149.7	146.3	139.3
Ht	0.52	0.51	0.49	0.48	0.48	0.48	0.50	0.48	0.50	0.49
Alanine	1.29	1.16	1.29	1.19	1.24	1.11	1.18	1.43	0.98	1.77

aminotrsanferase										
Alkaline phosphatase	1.29	1.26	1.24	1.14	1.80	0.94	1.10	1.11	0.96	1.17
Aspartate aminotransferase	1.62	1.29	1.51	1.25	1.67	1.14	1.22	1.57	1.16	1.21
cholinesterase	0.48	0.51	0.50	0.53	0.47	1.71	1.54	1.34	1.61	0.83
Leucine aminopeptidase	5.52	4.79	5.37	3.94	5.92	5.67	6.29	6.17	5.34	8.43
Gamma globulin	13.56	13.10	12.05	11.57	10.87	11.79	13.11	12.17	11.95	10.03

- *gross pathology findings:* Organ weight was examined and revealed few changes

Table 21 : Organ weight (in g or %)

		Males					Females				
Dose level (in ppm)		0	10	40	40	2000/1000	0	10	40	40	2000/1000
12 months											
Adrenal glands	Abs	0.064	0.063	0.060	0.056	0.052	0.083	0.084	0.093	0.091	0.083
	Rela	0.0110	0.0114	0.0110	0.0111	0.0115	0.0220	0.0246	0.0289	0.0236	0.0294
Brain	Abs	2.02	2.04	2.04	2.01	1.95	1.90	1.90	1.87	1.85	1.75
	Rela	0.350	0.368	0.375	0.399	0.432	0.512	0.557	0.581	0.480	0.629
Liver	Abs	23.8	24.1	19.5	17.1	21.8	13.3	15.4	13.1	13.8	15.8
	Rela	4.23	4.33	3.59	3.37	4.76	3.66	4.48	4.04	3.70	5.62
Spleen	Abs	0.825	0.907	0.801	0.805	0.779	0.690	0.747	0.621	0.665	0.544
	Rela	0.142	0.162	0.146	0.159	0.171	0.183	0.226	0.192	0.173	0.193
Thymus	Abs	0.162	0.169	0.139	0.152	0.137	0.138	0.109	0.126	0.107	0.126
	Rela	0.028	0.031	0.026	0.029	0.030	0.037	0.032	0.039	0.028	0.045
Testes ovary	Abs	3.86	3.89	3.93	3.87	3.67	0.102	0.102	0.118	0.097	0.082
	rela	0.67	0.70	0.72	0.76	0.81	0.0274	0.0302	0.0370	0.0253	0.0293
18 months											
Adrenal glands	Abs	0.084	0.068	0.071	0.100	0.057	0.098	0.113	0.094	0.110	0.070
	Rela	0.0192	0.0133	0.0140	0.0213	0.0146	0.0255	0.0325	0.0272	0.0331	0.0260
Brain	Abs	2.06	2.07	2.07	1.98	1.92	1.90	1.93	1.87	1.91	1.88
	Rela	0.459	0.399	0.396	0.412	0.474	0.504	0.563	0.538	0.578	0.704
Liver	Abs	22.5	22.9	21.7	20.3	20.0	16.0	15.5	16.4	14.5	13.8
	Rela	4.85	4.27	4.07	4.02	4.81	4.16	4.46	4.64	4.23	5.12
Spleen	Abs	0.866	0.788	0.975	0.767	0.794	0.715	0.790	0.701	0.695	0.609
	Rela	0.190	0.148	0.190	0.150	0.189	0.188	0.229	0.195	0.212	0.228
Thymus	Abs	0.121	0.103	0.131	0.139	0.105	0.085	0.095	0.073	0.106	0.131

	Rela	0.026	0.020	0.026	0.026	0.024	0.023	0.026	0.021	0.030	0.049
Testes ovary	Abs	3.46	3.79	3.95	3.65	3.25	0.107	0.107	0.100	0.112	0.090
	Rela	0.74	0.71	0.73	0.73	0.77	0.0280	0.0299	0.0291	0.0343	0.0333
Thyroid	Abs	0.046	0.041	0.044	0.075	0.048	0.038	0.042	0.036	0.050	0.049
	rela	0.0100	0.0077	0.0083	0.0159	0.0118	0.0100	0.0121	0.0102	0.0148	0.0183

- *histopathology findings:* the histopathological examination showed focal alteration in liver at 2000/1000 ppm.
- *mortality and time to death :* mortality was observed in all groups (see table 19)
- *reproductive parameters :* Reproductive parameters were examined. In females, follicular maturation and evolution of corpus luteum were unaffected. Moreover, in males, no effects on spermiogenesis were observed.

3.12.2 Human data

No information available

3.12.3 Other data

No information available

3.13 Aspiration hazard

Not evaluated in this CLH dossier.

4 ENVIRONMENTAL HAZARDS

Not evaluated in this CLH dossier.