CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: 1-vinylimidazole

EC Number: **214-012-0**

CAS Number: **1072-63-5**

Index Number: **--**

Contact details for dossier submitter: **BASF SE**
Postfach 67056
Ludwigshafen
Germany

Version number: 1 **Date:** **05/01/2016**

CONTENTS

Part A.

Part B.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***1-vinylimidazole***
EC number:	***214-012-0***
CAS number:	***1072-63-5***
Annex VI Index number:	***NA***
Degree of purity:	***≥ 99.5%***
Impurities:	***Impurities are not considered relevant for the classification and labelling of the substance.***

1.2 Harmonised classification and labelling proposal

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

	CLP Regulation
Current entry in Annex VI, CLP Regulation	No entry
Current proposal for consideration by RAC	Classification Repr. 1B, H360D Labelling GHS08 H360D, Dgr
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Classification Repr. 1B, H360D Labelling GHS08 H360D, Dgr

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				Conclusive but not sufficient for classification
2.2.	Flammable gases				Conclusive but not sufficient for classification
2.3.	Flammable aerosols				Conclusive but not sufficient for classification
2.4.	Oxidising gases				Conclusive but not sufficient for classification
2.5.	Gases under pressure				Conclusive but not sufficient for classification
2.6.	Flammable liquids				Conclusive but not sufficient for classification
2.7.	Flammable solids				Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures				Conclusive but not sufficient for classification
2.9.	Pyrophoric liquids				Conclusive but not sufficient for classification
2.10.	Pyrophoric solids				Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures				Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases				Conclusive but not sufficient for classification
2.13.	Oxidising liquids				Conclusive but not sufficient for classification
2.14.	Oxidising solids				Conclusive but not sufficient for classification
2.15.	Organic peroxides				Conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals				Conclusive but not sufficient for classification

3.1.	Acute toxicity - oral				**Not proposed in this CLH report**
	Acute toxicity - dermal				Conclusive but not sufficient for classification
	Acute toxicity - inhalation				Data lacking
3.2.	Skin corrosion / irritation				Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation				**Not proposed in this CLH report**
3.4.	Respiratory sensitisation				Data lacking
3.4.	Skin sensitisation				Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity				Conclusive but not sufficient for classification
3.6.	Carcinogenicity				Data lacking
3.7.	Reproductive toxicity	Repr. 1B, H360D			
3.8.	Specific target organ toxicity –single exposure				Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure				Conclusive but not sufficient for classification
3.10.	Aspiration hazard				Conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment				Conclusive but not sufficient for classification
5.1.	Hazardous to the ozone layer				Conclusive but not sufficient for classification

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

Labelling: Signal word:
Danger

Pictograms:
GHS08: Health hazard

Hazard statements:
H360D: May damage the unborn child.

Precautionary statements:
No subject for Annex entry.

Proposed notes assigned to an entry:

none

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

1-Vinylimidazole was not included in Annex I to Directive 67/548/EEC and has no entry in Annex VI Tables 3.1 and 3.2 of the Regulation (EC) No. 1272/2008/EC (GLP Regulation).

2.2 Short summary of the scientific justification for the CLH proposal

Toxicity to reproduction

Current classification: no classification in Annex VI of CLP

Proposed classification: Repr. 1B, H360D (CLP)

Developmental toxicity/teratogenicity

In a GLP compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD 422, the test compound 1-vinylimidazole was administered daily by gavage to groups of 10 male and 10 female Wistar rats to screen for potential reproductive and developmental toxicity. After a two-week premating period, these parental animals were mated and the females were allowed to give birth and bring up the offspring until sacrifice on PND 4. Analyses confirmed the overall accuracy of the prepared concentrations and the homogeneity of the test substance in the vehicle. The stability of these preparations was also demonstrated over a period of 7 days under ambient conditions.

In both male and female mid- and high-dose parental animals, piloerection and semiclosed eyelids were observed during premating. These are considered to be adverse clinical observations. Reduced food consumption was observed in the male and female parental animals at the mid- and high-doses (15 and 35 mg/kg bw/d) during various study phases. This resulted in statistically significantly decreased body weights and body weight gains in comparison to the controls. These effects, while significant, were considered to be treatment-related and adverse. Concerning clinical pathology no treatment-related, adverse effects were observed up to a dose of the compound of 35 mg/kg bw/day.

The test substance did not influence fertility.

The pups in the high-dose group (35 mg/kg bw/day) were much more likely to be stillborn, die, or be cannibalized in the first four days of life. As a result, both the live birth and viability indices were strongly reduced (74.5 and 59.6%, respectively). Together, these effects were judged to be both test substance-dependent and adverse.

In addition the pup body weights/weight gain were reduced at the 15 and 35 mg/kg bw/day dose. Upon gross pathological examination, a number of mid- and high-dose pups exhibited aneurysms of the great vessels of the heart. When these macroscopic alterations were examined microscopically in selected pups, histopathology revealed dissecting aneurysms in the dilated vessels (aorta, arteries or ductus arteriosus), which correlated overall with the macroscopic findings. The number of affected litters was two, both at 15 and 35 mg/kg bw/day. All of these findings are considered to be treatment-related and adverse.

Under the conditions of the present OECD 422 combined repeated dose toxicity study with the reproductive/developmental screening study, the NOAEL (no observed adverse effect level) for general parental toxicity is 5 mg/kg bw/day, based on adverse clinical symptoms and decreased body weights/body weight gain. The NOAEL for fertility 35 mg/kg bw/day (highest tested dose). The

NOAEL for developmental toxicity in the F1 offspring is 5 mg/kg bw/day, as decreased pup weights, perinatal mortality and dissecting aneurysms in the great vessels of the heart were noted at 15 mg/kg bw/day and above.

2.3 Current harmonised classification and labelling

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

No entry

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

Classification

Acute Tox. 4, H302

Eye damage 1, H318

Repr. 1B, H360D

Labelling

GHS05: corrosion

GHS07: exclamation mark

GHS08: health hazard

H302, H314, H360D, Dgr

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

1-Vinylimidzole is classified for reproductive toxicity, category 1B as it fulfils the criteria set out in Annex I, Chapter 3.7 of the Regulation 1272/2008/EC (CLP). Therefore, in line with Article 36 and 37 of the CLP, it should be subject to harmonised classification and labelling and a manufacturer, importer or downstream user of a substance may submit to the Agency a proposal for harmonised classification and labelling of that substance.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

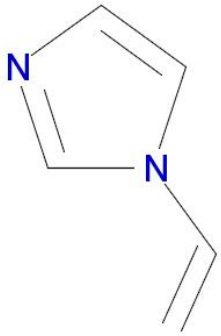
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC number:	214-012-0
EC name:	1-vinylimidazole
CAS number (EC inventory):	1072-63-5
CAS number:	1072-63-5
CAS name:	1-vinyl-1H-imidazole
IUPAC name:	1-vinyl-1H-imidazole
CLP Annex VI Index number:	--
Molecular formula:	C5H6N2
Molecular weight range:	94.1

Structural formula:



1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
1-vinylimidazole EC no: 214-012-0	≥ 99.5%	99 – 100%	

Current Annex VI entry: none

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Several	≤ 0.8 % (in total)	0 – 1.8%	

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
No additives	--	--	--	--

Current Annex VI entry: Not applicable.

1.2.1 Composition of test material

Not applicable

1.3 Physico-chemical properties

Table 8: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 1013 hPa	liquid	BASF SE, 2012	Visual inspection
Melting/freezing point	below -100 °C	BASF SE, 2012	Measured
Boiling point	192.1 °C at 1013.25 hPa (decomposes)	BASF AG, 1993	Measured
Relative density	1.04 g/cm^3 at 20 °C	BASF SE, 2012	Measured
Vapour pressure	0.38 hPa at 20 °C	BASF AG, 1993	Measured
Surface tension	Not surface active	--	Expert judgement
Water solubility	Miscible	GESTIS, 2011; Hommel, 2004	Measured
Partition coefficient n-octanol/water	0.54 at 25 °C	BASF AG, 1988	Measured
Flash point	81 °C	GESTIS, 2011; Hommel, 2004	Measured
Flammability	The substance is non-flammable upon ignition. The substance has no pyrophoric properties and does not liberate flammable gases on contact with water.	--	Expert judgement
Explosive properties	Non explosive	--	Expert judgement
Self-ignition temperature	415 °C	GESTIS, 2011; Hommel, 2004	Measured
Oxidising properties	No oxidising properties	--	Expert judgement
Granulometry	Not applicable	--	Substance is marketed or used in a non-solid or granular form.
Stability in organic solvents and identity of relevant degradation products	Not relevant	--	The stability of the substance is not considered as critical
Dissociation constant	5.62 at 20 °C	BASF SE, 2012	Measured
Viscosity	2.21 mPa·s (dynamic)	BASF SE, 2012	Measured

2 MANUFACTURE AND USES

2.1 Manufacture

1-Vinylimidazole is manufactured through reaction between imidazole with acetylene.

2.2 Identified uses

There are only industrial uses for 1-vinylimidazole, and no professional or consumer uses. 1-Vinylimidazole is used as a monomer for further polymerization. It has a high reactivity for radical polymerization. The polymerized product is used in different applications such as a lubricant, coating additive, emulsifier, polymer for metal ion filtration and in home care applications (dye transfer inhibition) and personal care applications (hair care).

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Based on the available information classification and labelling for physical-chemical properties according to Regulation 1272/2008/EC (CLP) is not justified.

4 HUMAN HEALTH HAZARD ASSESSMENT

Only the properties relevant to the proposed reproduction toxicity classification are described in detail.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

No information available.

4.1.2 Human information

No information available.

4.1.3 Summary and discussion on toxicokinetics

No data are available that describe the toxicokinetics of 1-vinylimidazole, therefore relevant substance properties and data from toxicity studies indicating systemic bioavailability were taken together to assess the general toxicokinetics of the substance.

1-vinylimidazole is a liquid with a molecular weight of 94.1 g/mol. The log Pow value is 0.54 and is completely miscible in water. A log Pow value between -1 and 4 favours absorption by passive diffusion. Furthermore, the molecular weight below 200 makes the test substance also favourable for absorption. The results of the acute oral (LD50 oral, rat: about 1040 mg/kg bw; BASF AG, 1953) and the repeated dose oral toxicity study with reproduction/developmental toxicity screening test indicate absorption of the test substance by the oral route. Overall, this suggests that 1-vinylimidazole may be readily absorbed by the gastrointestinal and respiratory tract.

The results of the acute dermal toxicity study (LD50 dermal, rat > 2000 mg/kg bw; BASF AG, 2005) do not indicate high absorption of the test substance by the dermal route. Furthermore, the QSAR model DERMWIN (part of the model EPI suite) results in an estimated Kp = 0.00202 cm/hr with log Kp = -2.80 + 0.66 log Kow – 0.0056 MW, indicating low dermal absorption (range: very low/low/moderate/high; Danish (Q)SAR Database, 2005).

4.2 Acute toxicity

Not evaluated in this dossier.

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

Not evaluated in this dossier.

4.4 Irritation

Not evaluated in this dossier.

4.5 Corrosivity

Not evaluated in this dossier.

4.6 Sensitisation

Not evaluated in this dossier.

4.7 Repeated dose toxicity

Only reproductive toxicity is assessed in this dossier. Two studies with repeated dose administration relevant for the assessment of reproductive toxicity are available for 1-vinylimidazole (table 9).

The toxicity after oral repeated exposure was investigated in a study conducted according to OECD Guideline 422 (BASF SE, 2013). Four groups of ten male and ten female Wistar rats were exposed to the test substance by oral gavage at 5, 15, or 35 mg/kg bw/d. Rats of the control groups, ten males and ten females, received the drinking water only. The duration of treatment covered a 2-week pre-mating and a mating period in both sexes. In males treatment lasted 30 days after beginning of administration of the test substance. Females were treated the entire gestation period as well as approximately 2 weeks of the lactation period. Females were sacrificed 50 days after beginning of administration of the test substance. During the study all parental animals were assessed for clinical observations, body weight and food consumption. A functional observation battery, a motor activity assay, and clinico-chemical and haematological examinations were performed in parental animals at the end of the administration period at day 28 in five male and at day 44 in 5 female animals per group. All parental animals were assessed by gross pathology and histopathological examination at the end of the study.

The main findings of systemic toxicity in this study can be found in tables 10a and 10b for males and females, respectively. There were no test substance-related mortalities in any of the male and female parental animals in any of the groups. During study week 1, one control female was sacrificed moribund. In both male and female mid- and high-dose parental animals, piloerection and semi closed eyelids were observed during pre-mating. One mid-dose female showed piloerection during postnatal days 1 and 2. No clinical signs of toxicity or changes of general behavior, which might have been attributed to the treatment were detected in the low-dose male or female generation parental animals during the whole study including gestation and lactation periods.

Food consumption of the mid and high dose F0 males was statistically significantly below control during the whole premating period (-9 and -17%). Food consumption of the high-dose F0 females was statistically significantly below control during premating days 0 - 13 (-15%), during GD 0 - 20 (-9%) and during the whole lactation period (-34%). The mid-dose F0 females showed statistically significantly reduced food consumption during the whole premating period (-12% below control). The reduced food consumption resulted in statistically significantly decreased terminal body weights in high dose males (-6%) and females (-10%) and reduced body weight gains only in males during premating (day 0-13) in the mid and high dose in comparison to the controls (-30 and -38%, respectively).

Table 9: Summary table of repeated dose toxicity after oral administration

Method	Results	Remarks	Reference
• Combined repeated dose and reproduction / developmental screening (oral: gavage) • Rat (Wistar) male/female • 5; 15; 35 mg/kg bw/day (actual ingested) • Exposure: covered a 2-week pre-mating and a mating period in both sexes (once daily at approximately the same time in the morning). In males treatment lasted 30 days after beginning of administration. Females were treated the entire gestation period as well as approximately 2 weeks of the lactation period. Females were sacrificed 50 days after beginning of administration. • OECD Guideline 422 • EPA, Health Effects Test Guidelines; OPPTS 870.3650 (July 2000)	• NOAEL: 5 mg/kg bw/day (actual dose received) Males/females: Based on adverse clincal symptoms and decreased body weights/body weight gain.	• 1 (reliable without restriction) • Key study • Experimental result • Test material (EC name): 1-vinylimidazole	BASF SE (2013)
• Subchronic (oral: gavage) • Rat (Wistar) male/female • 90 and 180 mg/kg (nominal in water) • Vehicle: distilled water • Similar to OECD Guideline 408, no clinical pathology conducted except investigation of γGT activity in liver homogenate, reproductive organs not examined, (histo) pathology was focussed on liver findings, other gross lesions were not further examined • Exposure: 3 months, the high dose was discontinued after 14 days for males and 21 days for females (5 days/week)	• LOAEL: 90 mg/kg bw/day (nominal) Males/females: Clinical signs; body weight; food and water consumption; clinical chemistry; organ weights, glandular stomach lesions in 2 females of the high dose group	• 2 (reliable with restrictions) • Supporting study • Experimental result • Test material (EC name): 1-vinylimidazole	BASF SE (1991)

No treatment-related changes among hematological parameters were observed. The few statistically significantly changed parameters in clinical chemistry are shown in table 11. At 15 and 35 mg/kg bw/d, alkaline phosphatase (ALP) activities were higher in females compared to controls, but the values were within the historical controls range (ALP: 0.39-0.87 µkat/L). In males of the mid test total bilirubin and albumin levels were increased. Both parameters were not anymore increased at the high dose. Some parameters were changed in males of all test groups, but the means were either within historical control ranges (for triglycerides and chloride; historical control range: triglycerides 0.41-1.32 mmol/L, chloride 99.9-107.4 mmol/L) or some means were marginally out of the historical control ranges, but the values were not changed dose-dependently (for potassium and inorganic phosphate; historical control range: potassium 4.35-4.95 mmol/L, inorganic phosphate 1.36-1.96 mmol/L). Therefore, all mentioned changes were regarded as incidental and not treatment-related. Urea levels in males at 15 and 35 mg/kg bw/d were higher compared to controls, but the values were not dose-dependently changed. The values were slightly above the historical control range (urea 4.91-7.42 mmol/L). However, this was the only relevantly altered parameter in these animals and therefore the change was regarded as treatment-related, but not adverse.

No treatment-related changes among urinalysis parameters were observed. In rats of both sexes (in females not statistically significantly) of all test groups, urine pH values were higher compared to controls. Probably due to precipitation in more alkaline urine, more crystals were found in the urine sediment of both sexes at the high dose and additionally in females of the mid dose (in males phosphate crystals, in females mainly unknown crystals). Phosphate crystals were normal in urine sediments of controls, and higher levels per se without any other alteration of urine parameters were regarded as treatment-related, but not adverse.

Pathological examination revealed centrilobular hepatocellular hypertrophy (grade 1 at the mid dose in males and at the high dose in females; grade 3 in the high dose males) correlating to statistically significant increased liver weights which was observed at the high dose group in females (+18%) and in mid and high dose males (+13 and +26%). This effect was assessed as adaptive and not adverse. The kidneys showed a weight increase in both high- and mid-dose males (+16 and +27%) and females (+10 and +15%). There were no histopathological findings correlating with this weight increase or to the crystals observed in urinalysis. The increased relative testes weights in males at the high dose (+13%) was related to the decreased terminal body weights in these animals. All other mean absolute and relative organ weight parameters did not show significant differences when compared to the control group. All other histopathological findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment.

Based on the adverse clinical symptoms and decreased body weights/body weight gain, the no observed adverse effect level (NOAEL) was set at 5 mg/kg bw/day.

Table 10a: Summary table of statistically significant, substance related findings in the F0 **males** of the OECD 422 study

	Control	**5 mg/kg bw/d**	**15 mg/kg bw/d**	**35 mg/kg bw/d**
Clinical observation during premating[1)]	0/10	0/10	1/10 (piloerection and semi closed eyelid)	5/10 (piloerection and 4/10 semi closed eyelid)
Food consumption/d during premating (d0-13) [2)]	22.9 ± 1.6	22.1 ± 0.8	20.8 ± 1.3** (-9%)	18.9 ± 1.3** (-17%)
Body weight [g] at pre-mating day 13 [2)]	343.3 ± 13.4	339.0 ± 8.4	332.1 ± 9.9	328.9 ± 15.5* (-4%)
Body weight [g] at post-mating day 0 (28 days of exposure) [2)]	376.9 ± 22.3	371.0 ± 13.2	358.6 ± 13.3	357.1 ± 19.3* (-5%)
Body weight changes [g] during pre-mating, day 0-13 [2)]	33.0 ± 10.1	28.4 ± 6.7	23.2 ± 7.4* (-30%)	20.3 ± 8.4** (-38%)
Absolute terminal body weight [g] [2)]	348.0 ± 23.4	342.4 ± 11.3	329.9 ± 14.1	327.6 ± 17.8* (-6%)
Absolute kidney weight [g] [2)]	2.008 ± 0.235	2.234 ± 0.099	2.242 ± 0.156	2.476 ± 0.176* (+23%)
Absolute liver weight [g] [2)]	7.120 ± 0.571	7.504 ± 0.335	7.732 ± 0.654	8.756 ± 0.814** (+23%)
Absolute testes weight [g] [2)]	3.373 ± 0.336	3.368 ± 0.215	3.344 ± 0.263	3.603 ± 0.252
Relative kidneys weight [%] [2)]	0.600 ± 0.062	0.651 ± 0.047	0.696 ± 0.303** (+16%)	0.761 ± 0.032** (+27%)
Relative liver weight [%] [2)]	2.126 ± 0.117	2.184 ± 0.061	2.399 ± 0.112* (+13%)	2.688 ± 0.096** (+26%)
Relative testes weight [%] [2)]	0.972 ± 0.113	0.984 ± 0.063	1.014 ± 0.067	1.102 ± 0.084** (+13%)
Hepatic centrilobular hypertrophy [1)]	0/10	0/10	9/10 (Grade 1)	10/10 (Grade 3)

[1)] Number of affected animals / total number per group.

[2)] Mean ± SD with * $p \leq 0.05$, ** $p \leq 0.01$; statistically significant differences compared to control group

Table 10b: Summary table of statistically significant, substance related findings in the F0 **females** of the OECD 422 study

	Control	**5 mg/kg bw/d**	**15 mg/kg bw/d**	**35 mg/kg bw/d**
Clinical observation during premating[1)]	1/10 (general poor condition, piloerection, labored respiration, sacrificed moribund	0/10	4/10 (piloerection), 3/10 (semi closed eyelid)	6/10 (piloerection and semi closed eyelid)
Clinical observation during lactation[1)]	0/8	0/9	1/9 (piloerection)	2/9 (complete litter loss)
Food consumption/d during premating[2)]	16.4 ± 1.1	15.5 ± 1.0	14.4 ± 0.8** (-12%)	13.9 ± 1.8** (-15%)
Food consumption/d during gestation (d0-20) [2)]	22.2 ± 1.6	22.6 ± 1.3	20.7 ± 1.9	20.2 ± 1.4* (-9%)
Food consumption/d during lactation (d1-4) [2)]	34.4 ± 4.3	31.9 ± 4.5	31.2 ± 5.9	22.8 ± 4.7** (-34%)
Body weight [g] at PND 0[2)]	264.4 ± 16.5	258.2 ± 11.6	248.3 ± 13.2* (-6%)	235.1 ± 9.2** (-11%)
Body weight [g] at lactation day 4[2)]	281.8 ± 17.0	270.8 ± 14.9	267.7 ± 14.3	224.2 ± 9.0** (-20%)
Absolute terminal body weight [g]	247.4 ± 14.8	235.2 ± 8.3	233.43 ± 10.8	222.7 ± 10.0** (-10%)
Relative kidneys weight [%]	0.656 ± 0 030	0.698 ± 0 038	0.722 ± 0.035* (+10%)	0.754 ± 0.049** (+15%)
Relative liver weight [%]	2.431 ± 0.126	2.597 ± 0.191	2.565 ± 0.145	2.869 ± 0.064** (+18%)
Hepatic centrilobular hypertrophy[1)]	0/10	0/10	0/10	9/10 (Grade 1)

[1)] Number of affected animals / total number per group.
[2)] Mean ± SD with * $p \leq 0.05$, ** $p \leq 0.01$; statistically significant differences compared to control group

Table 11: Summary table of statistically significant findings in clinical chemistry in the F0 **males** and **females** of the OECD 422 study

	Control	**5 mg/kg bw/d**	**15 mg/kg bw/d**	**35 mg/kg bw/d**
Males				
Urea (mmol/L) day 31 [mean ± SD]	6.02 ± 0.46	6.27 ± 0.50	8.00 ± 1.09**	7.54 ± 0.67*
Total bilirubin (µmol/L) day 31 mean ± SD]	1.92 ± 0.20	2.18 ± 0.28	2.67 ± 0.34**	2.18 ± 0.45
Albumin (g/L) day 31 [mean ± SD]	38.62 ± 0.60	39.27 ± 0.51	40.38 ± 0.76*	38.88 ± 1.09
Triglycerides (mmol/L) day 31 [mean ± SD]	0.35 ± 0.04	0.53 ± 0.07**	0.73 ± 0.23*	0.49 ± 0.10
K (mmol/L) day 31 [mean ± SD]	4.49 ± 0.19	5.03 ± 0.22*	4.83 ± 0.09*	4.95 ± 0.25*
Cl (mmol/L) day 31 [mean ± SD]	106 ± 0.8	104 ± 2.4*	103 ± 1.1**	101 ± 2.9**
Inorganic phosphate (mmol/L) day 31 [mean ± SD]	1.70 ± 0.10	2.01 ± 0.11**	1.94 ± 0.14*	2.08 ± 0.13**
Females				
ALP (µkat/L) day 50 [mean ± SD]	0.54 ± 0.05	0.66 ± 0.21	0.80 ± 0.12**	0.67 ± 0.05*

Mean ± SD with * $p \leq 0.05$, ** $p \leq 0.01$; statistically significant differences compared to control (Kruskal-Wallis + Wilcoxon test, two sided)

In an older GLP compliant 90-day toxicity study with a focus on effects on the liver, 10 Wistar rats per sex and dose were administered 1-vinylimidazole at 0, 90 and 180 mg/kg bw/day in water by gavage for 66 times (BASF SE, 1991). Feed and drinking water consumption, mortality, body weight, the state of health and clinical signs were checked regularly. At the end of the study, the determination of the γ-glutamyl transferase activity in the liver homogenate was carried out. No further clinical pathology was conducted. All animals were assessed by gross pathology, followed by a histopathological examination of the liver. Reproductive organs or other inner organs were not examined by histopathology in this study.

Slight to strong salivation was observed in the 90 mg/kg bw/day group, appearing transiently only within the first hour after administration. No other clinical signs were observed. The feed consumption in both male and female rats was reduced (males up to -42%, females up to -21%) and the drinking water consumption was increased (males up to 48%, females up to 105%). There was a delayed body weight gain in males only (at the end of the administration period - 31%). The liver weight in females was increased (+17 and +27% for absolute and relative weights respectively) and was decreased (absolute) in males (-33%). The surviving male and female animals of the 180 mg/kg bw/day group were sacrificed prematurely in cause of a strongly reduced general state and a decreased

feed consumption as well as a retarded body weight gain (male animals 14 days and female animals 21 days after the beginning of administration. An increase of the γ-glutamyl transferase activity in the liver homogenate of both sexes was found at day 14 in the males (+128 and 480%) and in females at day 21 (+238 and 280%) at the mid and high dose. There was no correlation between biochemical determination of γ-glutamyl transferase activity and histopathology as no adverse histopathological findings were observed in the liver. Based on the changes in liver enzyme activity, a lowest observed adverse effect level (LOAEL) of 90 mg/kg bw/day for males and females was set out in this study.

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

The hazard class is not evaluated in this dossier, but the information from the repeated dose toxicity studies is relevant for the assessment of reproductive toxicity (see above).

4.9 Germ cell mutagenicity (Mutagenicity)

Not evaluated in this dossier.

4.10 Carcinogenicity

No information available.

4.11 Toxicity for reproduction

The results of experimental studies are summarised in the following table:

Table 12: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
• Screening (oral: gavage) • Rat (Wistar) male/female • 0, 5, 15, 35 mg/kg bw/day (actual ingested) • Exposure: The duration of treatment covered a 2-week pre-mating and a mating period in both sexes (once daily at approximately the same time in the morning). In males treatment lasted 30 days after beginning of administration. Females were treated the entire gestation period as well as approximately 2 weeks of the lactation period. Females were sacrificed 50 days after beginning of administration. • OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)	• NOAEL (parental) (P): 5 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (Based on adverse clinical symptoms and decreased body weights/body weight gain.) • NOAEL (reproduction) (P): 35 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (No effects at the highest doses tested.) • NOAEL (developmental) (F1): 5 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (Decreased pup weights and dissecting aneurysms in the great vessels of the heart were noted at 15 mg/kg bw/d and above.)	• 1 (reliable without restriction) • Key study • Experimental result • Test material (EC name): 1-vinylimidazole	BASF SE (2013)

4.11.1 Effects on fertility

4.11.1.1 Non-human information

There is no one- or two-generation reproductive toxicity study available. However, in a GLP compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD 422, 1-vinylimidazole was given to rats by oral gavage (BASF SE, 2013). Groups of 10 male and 10 female Wistar rats received the test substance as an aqueous solution, at dose levels of 5, 15 and 35 mg/kg bw/day. Rats of the control group received the vehicle drinking water alone. The duration of treatment covered a 2-week pre-mating period and a mating period (max. of 2 weeks) in both sexes. In males treatment lasted 30 days after beginning of administration. Females were treated the entire gestation period as well as approximately 2 weeks of the lactation period. Females were sacrificed 50 days after beginning of administration. Analyses confirmed the overall accuracy of the prepared concentrations and the homogeneity of the test substance in the vehicle.

Further details of the main findings in parental animals can be found in Tables 10a and b in chapter 4.8.

There were no test substance-related mortalities in any of the male and female parental animals in any of the groups. During study week 1, one control female was sacrificed moribund. In both male

and female mid- and high-dose parental animals, piloerection and semiclosed eyelids were observed during pre-mating as signs of clinical toxicity.

Food consumption of the mid and high dose F0 males was statistically significantly below control during the whole premating period (-9 and -17%). Food consumption of the high-dose F0 females was statistically significantly below control during premating days 0 - 13 (-15%), during GD 0 - 20 (-9%) and during the whole lactation period (-34%). The mid-dose F0 females showed statistically significantly reduced food consumption during the whole premating period (-12% below control). The reduced food consumption resulted in statistically significantly decreased terminal body weights in high dose males (-6%) and females (-10%) and reduced body weight gains only in males during premating (day 0-13) in the mid and high dose in comparison to the controls (-30 and -38%, respectively).

Pathological examination revealed centrilobular hepatocellular hypertrophy (grade 1 in mid dose males and high dose females, grade 3 in high dose males) correlating to statistically significant increased liver weights which was observed at the high dose group in females (+18%) and in mid and high dose males (+13 and +26%). This effect was assessed as adaptive and not adverse. The kidneys showed a weight increase in both high- and mid-dose males (+16 and +27%) and females (+10 and +15%), but there were no histopathological findings in this organ. The increased relative testes weights in males at the high dose (+13%) was related to the decreased terminal body weights in these animals.

The summary of mating, reproduction and delivery data are shown in table 13. For all F0 parental animals which were placed with females to generate F1 pups copulation was confirmed. The male mating index was 100% in all groups including controls. One male in each group (control and dosed groups) did not generate F1 pups. Thus, the fertility index ranged between 90% and 88.9% without showing any relation to dosing. The apparently infertile male rats did not show relevant gross lesions. The weights of the testes and epididymides, necropsy findings at scheduled termination and histopathological examination of the sex organs (testes, epididymides, seminal vesicles, ovaries, uterus and vagina) revealed no treatment-related changes in the parental animals.

The female mating index calculated after the mating period for F1 litter was 100% in all test groups. The mean duration until sperm was detected varied between 1.9 and 3.0 days without any relation to dosing. All sperm positive rats delivered pups or had implants in utero with the exception of one animal in each group (control and dosed groups). The fertility index varied between 90% in all treated groups and 88.9% in control. None of the non-pregnant females had any relevant gross lesions. The mean duration of gestation was similar in all test groups (i.e. between 22.2 and 22.9 days). The gestation index was 100% in all test groups. Implantation was not affected by the treatment since the mean number of implantation sites was comparable between all test substance-treated groups and the controls, taking normal biological variation into account. There were no biologically significant differences in post-implantation loss between the groups (3.5% / 6.7% / 3.3% / 11.6%), and the mean number of F1 pups delivered per dam remained unaffected (11.1 / 10.1 / 11.8 and 10.4 pups/dam at 0, 5, 15 and 35 mg/kg bw/d). The rate of liveborn pups was considerably reduced in the high-dose group (35 mg/kg bw/d), as indicated by a reduced live birth index (100% at 5 mg/kg bw/day, 98.9% in controls, 94.3% at 15 mg/kg bw/day and 74.5% at 35 mg/kg bw/day. Moreover, the number of stillborn pups was significantly increased in the high-dose group (1 / 0 / 6 / 24 pups/dam for controls, low, mid and high dose). The increased number of stillborn pups can be explained by the teratogenic effects at the high dose which is described more in detail in section 4.11.2 (Developmental toxicity).

In summary, it can be concluded that under the conditions of this combined repeated dose toxicity study with the reproduction/developmental toxicity screening test the oral administration by gavage of 1-vinylimidazole to male and female Wistar rats resulted in signs of systemic toxicity (clinical

signs, reduced body weight and food consumption in parental females; NOAEL 5 mg/kg bw/d). The male and female mating and fertility indices, the pre-coital time, the gestation index, the post-implantation loss, the litter size and the sex ratio were not affected by treatment. The NOAEL for fertility impairing effects can therefore set at the highest tested dose (35 mg/kg bw/d).

Table 13: Mating, reproduction and delivery data

	Control	**5 mg/kg bw/d**	**15 mg/kg bw/d**	**35 mg/kg bw/d**
No. of females mated	9	10	10	10
No. of females pregnant	8	9	9	9
Female/male mating index [%]	100	100	100	100
Female/male fertility index [%]	88.9	90.0	90.0	90.0
Mating days until day 0 pc [mean]	1.9	2.4	2.4	3.0
No. dams with liveborn pups [%]	8 (100%)	9 (100%)	9 (100%)	9 (100%)
No. dams with total litter loss [%]	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No. dams with stillborn pups	1 (12.5%)	0 (0%)	1 (11.1%)	6 (66.7%)
Total no. of liveborn pups (Live birth index)	88 (98.9%)	91 (100%)	100 (94.3%)	70 ** (74.5%)
Total no. of still born pups	1 (1.1%)	0 (0%)	6 (5.7%)	24 (25.5%) **
Gestation days [mean ± SD]	22.2 ± 0.5	22.3 ± 0.5	22.6 ± 0.5	22.9 ± 0.8
Implantations/dam [mean ± SD]	11.5 ± 2.3	11.0 ± 3.6	12.2 ± 2.4	11.9 ± 1.3
Post implantation loss per group (ratio dead implants/total implants) [mean %]	3.53	6.66	3.34	11.57
Pups delivered/dam (viable and stillborn) [mean ± SD]	11.1 ± 2.4	10.1 ± 3.1	11.8 ± 2.1	10.4 ± 2.0
Sex ratio [% live males day 0]	56.8	48.4	47.0	57.1

*$p \leq 0.05$, ** $p \leq 0.01$ (Dunnett test, two-sided)), statistically significant differences compared to control group

4.11.1.2 Human information

No information available.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

A prenatal developmental toxicity study is not available. However, in the above described combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD 422, 1-vinylimidazole was given to rats by oral gavage (BASF SE, 2013). Groups of 10 male and 10 female Wistar rats received the test substance as an aqueous solution, at dose levels of 5, 15 and 35 mg/kg bw/day. Rats of the control group received the vehicle drinking water alone. The duration of treatment covered a 2-week pre-mating period and a mating period (max. of 2 weeks) in both sexes. In males treatment lasted 30 days after beginning of administration. Females were treated the entire gestation period as well as approximately 2 weeks of the lactation period. Females were sacrificed 50 days after beginning of administration.

The treatment resulted in significant parental toxicity at the high and mid-dose (piloerection and semiclosed eyelids, reduced food consumption and body weights, as well as body weight gain). Further details regarding parental effects can be found in the above described section 4.8. Pathological examination in parental animals revealed centrilobular hepatocellular hypertrophy correlating to statistically significant increased relative liver weights in males at the mid and high dose and at the high dose females. The kidneys showed an increase in relative weight in both high- and mid-dose males and females without a histopathological finding.

The summary litter report and the pup status can be found in table 14. The pups in the high-dose group were much more likely to be stillborn, dead, or be cannibalized in the first four days of life. As a result, both the live birth index and viability index were strongly reduced (74.5% and 59.6%, respectively). Together, these effects were judged to be test substance-dependent and adverse. At the low and mid dose, the mean number of delivered F1 pups per dam and the rates of liveborn and stillborn F1 pups were comparable to the controls. The sex distribution and sex ratios of live F1 pups on the day of birth and PND 4 did not show substantial differences between the control and the test substance-treated groups.

The summary of the pathological examination of the foetuses is shown in table 15. All pups with scheduled sacrifice on PND 4 and all stillborn pups were examined externally and their organs were assessed macroscopically. All stillborn pups and all pups that died before PND 4 were examined externally. Mean body weight of the mid- and high-dose pups and body weight gain between postnatal day 1 and day 4 of the high-dose pups were statistically significantly reduced. These effects are considered treatment-related and adverse. Clinical observations of pups revealed no substance-related changes. Upon gross pathological examination of the pups, a number of mid- and high-dose pups exhibited aneurysms of the great vessels of the heart. All pups with macroscopically dilated pericardial vessels from the mid and high dose group were processed histotechnically stained with Hart/Masson-Goldner Trichrome and examined histopathologically for the presence of aneurysms. Microscopic examination of these macroscopic alterations revealed dissecting aneurysms in the dilated vessels (aorta, arteries or ductus arteriosus), which correlated overall with the macroscopic findings. The number of affected litters was two in both the mid- and high-dose group. All pups selected for microscopic examination displayed dilated vessels. At the high dose, all pups with a dilated aortic arched showed also a dilated aorta. At the mid dose, from the 3 pups with a dilated

aortic arch this finding coincided only in one pup of the 3 pups with a dilated aorta. All of these findings in pups were ascribed to treatment and considered to be adverse.

Table 14 Summary litter report and the pup status

	Control	**5 mg/kg bw/d**	**15 mg/kg bw/d**	**35 mg/kg bw/d**
Total No. of litters	8	9	9	9
With liveborn pups	8 (100%)	9 (100%)	9 (100%)	9 (100%)
With stillborn pups	1 (12.5%)	0 (0%)	1 (11.1%)	6 (66.7%)
Implantation sites/dam [mean ± SD]	11.5 ± 2.3	11.0 ± 3.6	12.2 ± 2.4	11.9 ± 1.3
Post implantation loss per test group (ratio dead implants/total implants) [mean %]	3.53	6.66	3.34	11.57
Pups delivered/dam (viable and stillborn) [mean ± SD]	11.1 ± 2.4	10.1 ± 3.1	11.8 ± 2.1	10.4 ± 2.0
Viable litter size day 0 [mean ± SD]	11.0 ± 2.2	10.1 ± 3.1	11.1 ± 2.6	7.8 ± 3.3
Viable litter size day 4 [mean ± SD]	11.0 ± 2.2	10.0 ± 2.9	10.3 ± 2.9	5.7 ± 4.3**
Total no. of liveborn pups (Live birth index)	88 (98.9%)	91 (100%)	100 (94.3%)	70** (74.5%)
Total no. of stillborn pups	1 (1.1%)	0 (0%)	6 (5.7%)	24 (25.5%)**
Perinatal loss per group (= %stillborn/delivered x 100) [mean %]	0.89	0	5.13	27.29
No. of pups surviving days 0 to 4	88	90	93	51
Viability index [mean% ± SD] (no. live pups on day 4 / no live pups/day of birth)	100 ± 0	99.3 ± 2.2	92.3 ± 15.9	59.6 ± 43.1**
Sex ratio [% live males day 0]	56.8	48.4	47.0	57.1

*$p \leq 0.05$, ** $p \leq 0.01$ (Dunnett test, two-sided), statistically significant differences compared to control group

Table 15: Summary of pathology examination pups
(pathological examination performed in both viable and all stillborn pups)

	Control	**5 mg/kg bw/d**	**15 mg/kg bw/d**	**35 mg/kg bw/d**
No. of litters evaluated	8	9	9	9
No. of pups evaluated	89	91	106	94
No. of pups with signs per group (all necropsy observations incl. post mortem autolysis, empty stomach, cannibalized pups, any organ findings)	1	2	10	39
No. pups with dilated aorta (thereof in stillborn pups)	0	0	1 (1)	7 (4)
Affected litters with pups with dilated aorta (%) [mean incidence per litter]	0%	0%	11% (0.11)	22% (0.77)
No. pups with dilated aortic arch (thereof in stillborn pups)	0	0	3 (1)	3 (2)
Affected litters with pups with dilated aortic arch (%) [mean incidence per litter]	0	0	2 (22%) (0.33)	2 (22%) (0.33)
No. pups with dilated ductus arteriosus	0	0	1	0
No. of pups with dilated subclavian artery	0	0	0	1
No. of pups with empty stomachs	0	0	0	11
Pup weight day 1 (g) (all viable pups) [mean% ± SD]	7.1 ± 0.9	7.2 ± 0.8	6.1 ± 0.6*	5.9 ± 0.7*
Pup weight gain (g) (PND1 to PND4) [mean% ± SD]	3.9 ± 0.8	3.8 ± 0.9	3.4 ± 0.8	2.1 ± 1.6**

*$p \leq 0.05$, ** $p \leq 0.01$ (Dunnett test, two-sided), statistically significant differences compared to control group

In summary, under the conditions of this combined repeated dose toxicity study with the reproduction/developmental toxicity screening test the oral administration by gavage of 1-vinylimidazole to male and female Wistar rats resulted in signs of systemic toxicity (clinical signs, reduced body weight and food consumption in parental females) at the high and mid dose, a reduced live birth index and a reduced viability index at the high dose. Dissecting aneurysms in the great vessels of the heart were observed from the mid-dose level onwards.

The NOAEL developmental toxicity was 5 mg/kg bw/day based on decreased pup weights, perinatal mortality and dissecting aneurysms in the great vessels of the heart at 15 mg/kg bw/day and above. These effects on pup weight and the great vessels of the heart are not considered to be secondary to the effects observed at 15 mg/kg bw/d or higher in the parental animals (slight reduced body weight and food consumption).

4.11.2.2 Human information

No information available.

4.11.3 Other relevant information

No information available.

4.11.4 Summary and discussion of reproductive toxicity

In a GLP compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD 422, the test compound 1-vinylimidazole was administered daily by gavage to 10 Wistar rats per sex and dose (0, 5, 15, 35 mg/kg bw/d) to screen for potential reproductive and developmental toxicity. After a two-week premating period, these parental animals were mated and the females were allowed to give birth and bring up the offspring until sacrifice on PND 4. Analyses confirmed the overall accuracy of the prepared concentrations and the homogeneity of the test substance in the vehicle.

In both male and female mid- and high-dose parental animals adverse clinical observations (piloerection and semiclosed eyelids) were observed during premating. Reduced food consumption resulting in decreased body weights and body weight gains was observed in the male and female parental animals at the mid- and high-doses during various study phases. Regarding pathology, adaptive, but non-adverse effects were observed in liver and kidney.

The test substance did not influence fertility.

The pups in the high-dose group (35 mg/kg bw/day) were much more likely to be stillborn, dead, or be cannibalized in the first four days of life. As a result, both the live birth and viability indices were strongly reduced (74.5 and 59.6%, respectively). Together, these effects were judged to be both test substance-dependent and adverse.

In addition the pup body weights/weight gain were reduced at the 15 and 35 mg/kg bw/day dose. Upon gross pathological examination, a number of mid- and high-dose pups exhibited aneurysms of the great vessels of the heart. When these macroscopic alterations were examined microscopically in selected pups, histopathology revealed dissecting aneurysms in the dilated vessels (aorta, arteries or ductus arteriosus), which correlated overall with the macroscopic findings. The number of affected litters was two both at 15 and 35 mg/kg bw/day. All of these findings are considered to be treatment-related and adverse.

Under the conditions of the present OECD 422 combined repeated dose toxicity study with the reproductive/developmental screening study, the NOAEL (no observed adverse effect level) for general parental toxicity is 5 mg/kg bw/day, based on adverse clinical symptoms and decreased body weights/body weight gain. The NOAEL for fertility impairing effects is 35 mg/kg bw/d which is the highest dose tested in this study. The NOAEL for developmental toxicity in the F1 offspring is 5 mg/kg bw/day, as decreased pup weights, perinatal mortality and dissecting aneurysms in the great vessels of the heart were noted at 15 mg/kg bw/day and above.

4.11.5 Comparison with criteria

According to CLP chapter 3.7.1 substances are classified for reproductive toxicity for adverse effects on sexual function and fertility, as well as developmental toxicity in the offspring and effects on or via lactation.

This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

For the classification of a substance in Category 1B “Presumed human reproductive toxicant”, largely based on animal data, studies shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 “Suspected human reproductive toxicant” may be more appropriate. The classification in Category 1A “Known or presumed human reproductive toxicant” is largely based on evidence from humans.

Classification for effects on or via lactation is intended to indicate when a substance may cause harm due to its effects on or via lactation, and it is independent of consideration of the reproductive toxicity of the substance. According to Table 3.7.1 (b) of the CLP-regulation, classification for effects on or via lactation can be assigned on the:
a) human evidence indicating a hazard to babies during the lactation period; and/or
b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or
c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

Assessment of the potential of 1-vinylimidazole to impair fertility is based on results from a reliable reproduction/developmental toxicity screening test according to OECD 422. There were no indications of reproduction toxicity up to the highest dose level of 35 mg/kg bw/day with a thorough histopathological examination of all male and female reproductive organs. This dose resulted in systemic toxicity as indicated by clinical signs, reduced body weight, food consumption and adaptive pathological changes in liver in parental females. There were no differences in mating and fertility indices, the pre-coital time, the gestation index, the post-implantation loss, the litter size and the sex ratio were not changed compared to the control animals. Therefore, the substance does not meet the criteria for reproductive toxicity category 1 or 2 (i.e. evidence from humans or animals relevant for toxicity assessment in humans).

1-Vinylimidazole caused developmental toxicity and teratogenicity in a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422. Severe effects on embryo-fetal development including increased pup mortality at delivery and during lactation, decreased pup weights and an increased rate of malformations in the pericardial

vessels at the mid and high dose (15 and 35 mg/kg bw/d) were observed. According to the CLP regulation, adverse effects on development include (1) death of the developing organism (2) structural abnormality (2) altered growth, and (4) functional deficiency. The observed effects for 1-vinylimidazole fall at least into the categories 1 - 3 of these manifestations and are therefore considered to be clear evidence of an adverse impact on development. The extent of systemic toxicity induced in the F0 generation in the mid and high dose group (moderately decreased food consumption during gestation period, reduced body weights in females during lactation, minimal to moderate centrilobular hepatocellular hypertrophy) is not considered to be attributable to the severe degree of toxicity in the offspring (teratogenicity).

Therefore, based on CLP criteria the substance shall be placed in category 1B (H360D) for reproductive toxicity because there is clear evidence from animal studies of an adverse effect on development. There is no mechanistic information available raising doubt about the relevance of the effect for humans. Thus, classification in Category 2 “Suspected human reproductive toxicant” would not be appropriate. As there is no evidence for developmental toxic effects in humans, the classification in Category 1A “Known or presumed human reproductive toxicant” is also not justified.

It is not possible to assess the effects of the substance on or via lactation due to the experimental design of the study (e.g. pups only investigated until day 4 postnatally, no information on presence of substance or metabolites in milk, measurement of milk yield not studied) although the findings maybe mainly attributed to the teratogenic and fetotoxic potential of 1-vinylimidazole. Based on currently available data, classification for effects on or via lactation is therefore not warranted.

4.11.6 Conclusions on classification and labelling

The substance does not meet the criteria for classification in Category 1A, 1B or 2 for adverse effects on sexual function and fertility.

Based on clear evidence for development toxicity in an animal study as indicated by increased pup mortality, decreased pup weights and dissecting aneurysms in the great vessels of the heart, 1-vinylimidazole may cause damage to the unborn child and is classified and labelled Repr. 1B (H360D) according to Regulation 1272/2008/EC. A specific concentration limit for developmental toxicity is not proposed.

Based on currently available data, classification for effects on or via lactation is therefore not warranted.

1-Vinylimidazole has not been included Annex VI Tables 3.1 and 3.2 of the Regulation 1272/2008/EC.

4.12 Other effects

Not evaluated in this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier. No classification and labelling proposed based on available data.

6 OTHER INFORMATION

This substance has been registered according to the requirements of the REACH legislation.

7 REFERENCES

BASF AG (1953). Bericht über die gewerbetoxikologische Prüfung von n-Vinylimidazol. Testing laboratory: BASF AG, Department of Toxicology. Report no.: I/261. Owner company: BASF SE. Report date: 1953-02-16.

BASF AG (1988). Bestimmung des Verteilungskoeffizienten log Pow von Vinylimidazol in 1-Octanol/Wasser bei 25 °C. Testing laboratory: Department of central analytics. Report no.: 102707/01. Owner company: BASF SE. Report date: 1988-12-29.

BASF AG (1991). Study of the oral toxicity of 1-Vinylimidazol dest. (unstabilized) in Wistar Rats administration by gavage for 3 months (66 administrations). Testing laboratory: BASF AG, Department of Toxicology, D-W6700 Ludwigshafen, Germany. Report no.: 35S0570/85133. Owner company: BASF SE. Report date: 1991-01-29.

BASF AG (1993). Dampfdruck von 1-Vinylimidazol. Testing laboratory: Department of central analytics. Report no.: BRU 93.390. Owner company: BASF SE. Report date: 1993-12-10.

BASF AG (2005). Report 1-Vinylimidazol - Acute dermal toxicity study in rats. Testing laboratory: Department of Toxicology and Ecotoxicology, BASF AG, 67056 Ludwigshafen/Rhein, Germany. Report no.: 11A0335/001154. Owner company: BASF SE. Report date: 2005-04-25.

BASF SE (2012). Physico-chemical properties of "1-Vinylimidazol". Testing laboratory: Competence Center Analytics, BASF SE, D-67056 Ludwigshafen. Report no.: 11L00236. Owner company: BASF SE. Report date: 2012-01-06.

BASF SE (2013). 1-Vinylimidazol Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in Wistar Rats Oral Administration (Gavage). Testing laboratory: BASF SE Experimental Toxicology and Ecology, 67056 Ludwigshafen, Germany. Report no.: 85R0335/00R021. Owner company: BASF SE, 67056 Ludwigshafen, Germany. Report date: 2013-05-15.

Danish (Q)SAR Database (http://qsar.food.dtu.dk/), Information on the models used (PDF): “User Manual for the Internet Version of the Danish (Q)SAR Database, Databse Version 1, May 2005, http://qsar.food.dtu.dk/User_Manual_Danish_Database.pdf; last access: 2014-01-22.

GESTIS – Substance Database (2011). 1-Vinylimidazol. GESTIS - Substance Database (Information system on hazardous substances of the Berufsgenossenschaften) as cited 23.03.2011.

Hommel (2004). 1-Vinylimidazol, Merkblatt 2452. Handbuch der gefährlichen Güter © by Springer-Verlag Berlin Heidelberg 2004.