CLH report

Proposal for Harmonised Classification and Labelling

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

Pymetrozine (ISO);

(E)-4,5-dihydro-6-methyl-4-(3-pyridylmethyleneamino)-1,2,4-triazin-3(2H)-one

EC Number: **-**

CAS Number: **123312-89-0**

Index Number: **613-202-00-4**

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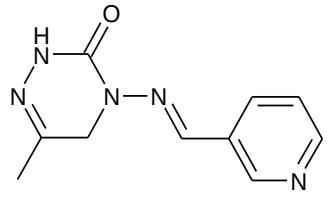
CONTENTS

1. IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

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

Name(s) in the IUPAC nomenclature or other international chemical name(s)	(E)-4,5-dihydro-6-methyl-4-(3-pyridylmethyleneamino)-1,2,4-triazin-3(2H)-one
Other names (usual name, trade name, abbreviation)	-
ISO common name (if available and appropriate)	pymetrozine
EC number (if available and appropriate)	-
EC name (if available and appropriate)	-
CAS number (if available)	123312-89-0
Other identity code (if available)	-
Molecular formula	$C_{10}H_{11}N_5O$
Structural formula	
SMILES notation (if available)	
Molecular weight or molecular weight range	
Degree of purity (%) (if relevant for the entry in Annex VI)	≥ 95.0 %

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self- classification and labelling (CLP)**
(E)-4,5-dihydro-6-methyl-4-(3-pyridylmethyleneamino)-1,2,4-triazin-3(2H)-one	***≥ 95.0 %***	Carc. 2 – H351 Aquatic Chronic 3 – H412	Carc. 2, H351 Aquatic Chronic 3, H412 Acute Tox. 4, H332 Carc. 2, H351 Aquatic Chronic 3, H412 Carc. 2, H351 Aquatic Chronic 3, H412

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

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
confidential				

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

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
confidential					

Table 5: Test substances (non-confidential information)

Identification of test substance	**Purity**	**Impurities and additives (identity, %, classification if available)**	**Other information**
confidential			

2. PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	***613-202-00-4***	***pymetrozine (ISO) (E)-4,5-dihydro-6-methyl-4-(3-pyridylmethyleneamino)-1,2,4-triazin-3(2H)-one***	-	***123312-89-0***	Carc. 2 Aq. Chronic 3	H351 H412	GHS08 Wng	H351 H412			
Dossier submitters proposal					**Add** Repr. 2 **Modify** Aq. Chronic 1	**Add** H361fd **Modify** H410	GHS08 Wng **Add** GHS09	**Add** H361fd **Modify** H410		M=1	
Resulting Annex VI entry if agreed by RAC and COM					Carc. 2 Repr. 2 Aq. Chronic 1	H351 H361fd H410	GHS08 GHS09 Wng	H351 H361fd H410		M=1	

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

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	*data conclusive but not sufficient for classification*	Yes
Flammable gases (including chemically unstable gases)	*data lacking*	No
Oxidising gases	*data lacking*	No
Gases under pressure	*data lacking*	No
Flammable liquids	*data lacking*	No
Flammable solids	*data conclusive but not sufficient for classification*	Yes
Self-reactive substances	*data lacking*	No
Pyrophoric liquids	*data lacking*	No
Pyrophoric solids	*data lacking*	No
Self-heating substances	*data lacking*	No
Substances which in contact with water emit flammable gases	*data lacking*	No
Oxidising liquids	*data lacking*	No
Oxidising solids	*data conclusive but not sufficient for classification*	Yes
Organic peroxides	*data lacking*	No
Corrosive to metals	*data lacking*	No
Acute toxicity via oral route	*hazard class not assessed in this dossier*	No
Acute toxicity via dermal route	*hazard class not assessed in this dossier*	No
Acute toxicity via inhalation route	*hazard class not assessed in this dossier*	No
Skin corrosion/ irritation	*hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation	*hazard class not assessed in this dossier*	No
Respiratory sensitisation	*hazard class not assessed in this dossier*	No
Skin sensitisation	*hazard class not assessed in this dossier*	No
Germ cell mutagenicity	*hazard class not assessed in this dossier*	No
Carcinogenicity	*harmonised classification (proposed and) available*	Yes
Reproductive toxicity	*harmonised classification proposed*	Yes
Specific target organ toxicity-single exposure	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-repeated exposure	*hazard class not assessed in this dossier*	No
Aspiration hazard	*hazard class not assessed in this dossier*	No
Hazardous to the aquatic environment	*harmonised classification proposed*	Yes
Hazardous to the ozone layer	*hazard class not assessed in this dossier*	No

3. HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

No data on the discussions during the C&L procedure of the ECB.

During the PPP procedure it was discussed, whether there is a need for classification as a reproductive toxicant (Pesticides peer review meeting 114). The report states:

> *"From the available data, adverse findings in testes were observed mainly in short term studies (effects on hormonal levels and testes at 255 mg/kg bw per day in 28-d rat study; effects in testes at 61 mg/kg bw per day in 28-day dog, at 14 mg/kg bw per day in 90-day dog and at 5 mg/kg bw per day in 1-year dog). In the multigeneration study, there was no effect on reproduction/fertility up to the high dose (110 mg/bw per day), but the testes were not examined histopathologically.*
>
> *The applicant's hypothesis that the testes findings are secondary to systemic toxicity (liver) is not supported by the experts.*
>
> *One expert highlighted that substances have already been classified for effects on reproductive organs without effect on fertility. It was noted that changes were also observed in uterus (dogs and mice).*

> *The majority of experts agreed to propose classification* ***Repr. Cat. 2*** *(H361f Suspected of damaging fertility), on the basis of the overall findings in reproductive organs in rats, dogs and mice."*

During the pesticides peer-review procedure it was discussed, whether there is a need for classification as a developmental toxicant (Pesticides peer review meeting 114). The report states:

> *"Since similar malformations are observed in 2 species, it was mentioned that this could trigger a classification in category 1. Taking into account the high maternal toxicity in one species and the absolute number of findings (limited), the experts agreed to propose* ***Repr. Cat. 2*** *(H361d Suspected of damaging the unborn child)."*

4. JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Pymetrozine is an active substance in the meaning of Directive 91/414/EEC (repealed by the Regulation EC 1107/2009).

5. IDENTIFIED USES

Pymetrozine is an insecticide used in agriculture, for ornamental plant and market gardening.

6. DATA SOURCES

Main data source for the evaluation of the toxicological properties of pymetrozine were Volumes 1 and 3 of the revised Renewal Assessment Report (RAR) dated 27 February 2014, which was prepared for the pesticides procedure. It is attached to the CLH dossier in its final version „Final Addendum to the Renewal Assessment Report" (available at EFSAs website). In April 2015, the applicant submitted additional toxicological studies and statements intended to support the preparation of this CLH dossier. These were taken into account and integrated in the dossier. All toxicological studies included in this dossier were evaluated and assessed by the dossier submitter.

7. PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or stimated)
Physical state at 20°C and 101,3 kPa	Solid		Visual assessment
Melting/freezing point	217°C	Rodler, 1993	Measured
Boiling point	190°C (decomposition)	Rodler, 1993	Measured
Relative density	1.37	Fueldner, 1995	Measured
Vapour pressure	< 4.2 x 10–6 Pa (25 °C)	Geoffroy, 1993	Measured
Surface tension	69.4 -72.3 mN/m (10 g/l at 20 °C)	Ryser, 1994	Measured
Water solubility	320 mg/L (25 °C; pH 5) 270 mg/L (25 °C; pH 7) 270 mg/L (25 °C; pH 9)	Stulz, 1995	Measured
Partition coefficient n-octanol/water	log Po/w = -0.24 (25 °C; pH 5) log Po/w = -0.19 (25 °C; pH 7) log Po/w = -0.20 (25 °C; pH 9)	Stulz, 1995	Measured
Flash point			Not applicable (melting point > 40 °C)
Flammability	Not highly flammable	Schürch, 1993	estimated
Explosive properties	Not explosive	Schürch, 1993	Measured
Self-ignition temperature	No self-ignition up to 400 °C.		
Oxidising properties	Non-oxidising	Schürch, 1993	Measured
Granulometry	Data lacking		
Stability in organic solvents and identity of relevant degradation products	Data lacking		
Dissociation constant	pKa = 4.06	Jäckel, 1993	Measured
Viscosity	Data lacking		

8. EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Table 9: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
EEC A 14	Not explosive		Schürch, 1993

8.1.1 Short summary and overall relevance of the provided information on explosive properties

There are no effects after burning, shock or friction.

8.1.2 Comparison with the CLP criteria

Data conclusive but not sufficient for classification.

8.1.3 Conclusion on classification and labelling for explosive properties

Pymetrozine has no explosive properties.

8.2 Flammable gases (including chemically unstable gases)

8.3 Oxidising gases

8.4 Gases under pressure

8.5 Flammable liquids

8.6 Flammable solids

Table 10: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
EEC A 10	Not highly flammable		Schürch, 1993

8.6.1 Short summary and overall relevance of the provided information on flammable solids

Ignition with a hot platinum wire results in melting of the substance. The molten substance does not sustain a flame.

8.6.2 Comparison with the CLP criteria

Data conclusive but not sufficient for classification.

8.6.3 Conclusion classification and labelling for flammable solids

Pymetrozine is not highly flammable.

8.7 Self-reactive substances

8.8 Pyrophoric liquids

8.9 Pyrophoric solids

8.10 Self-heating substances

8.11 Substances which in contact with water emit flammable gases

8.12 Oxidising liquids

8.13 Oxidising solids

Table 11: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
EEC A 17	Non-oxidising		Schürch, 1993

8.13.1 Short summary and overall relevance of the provided information on oxidising solids

The burning rate of the reference mixture and the test mixture result in non-oxidising properties for Pymetrozine.

8.13.2 Comparison with the CLP criteria

Data conclusive but not sufficient for classification.

8.13.3 Conclusion on classification and labelling for oxidising solids

Pymetrozine has no oxidising properties.

8.14 Organic peroxides

8.15 Corrosive to metals

9. TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

This section contains a short summary taken from Volume 1 (chapter 2.6) of the Renewal Assessment Report (RAR), which was written for the pesticides procedure. In case more detailed information on the reported findings is needed, it is referred to the confidential annex to this document or to Volume 3 / chapter B.6 of the RAR.

Following oral administration to rats, pymetrozine was rapidly and almost completely absorbed from the gastrointestinal tract into the general circulation. Independent of the label, maximum concentrations in the blood were reached between 15 minutes and 1 hour after administration at the low dose level (0.5 mg/kg bw) and between 4 and 8 hours after administration at the high dose level (100 mg/kg bw).

The extent of absorption from the intestinal tract (based on renal and biliary excretion and on the amount remaining in the carcass) was about 90 % at the low dose and about 82 % at the high dose, independent of the label.

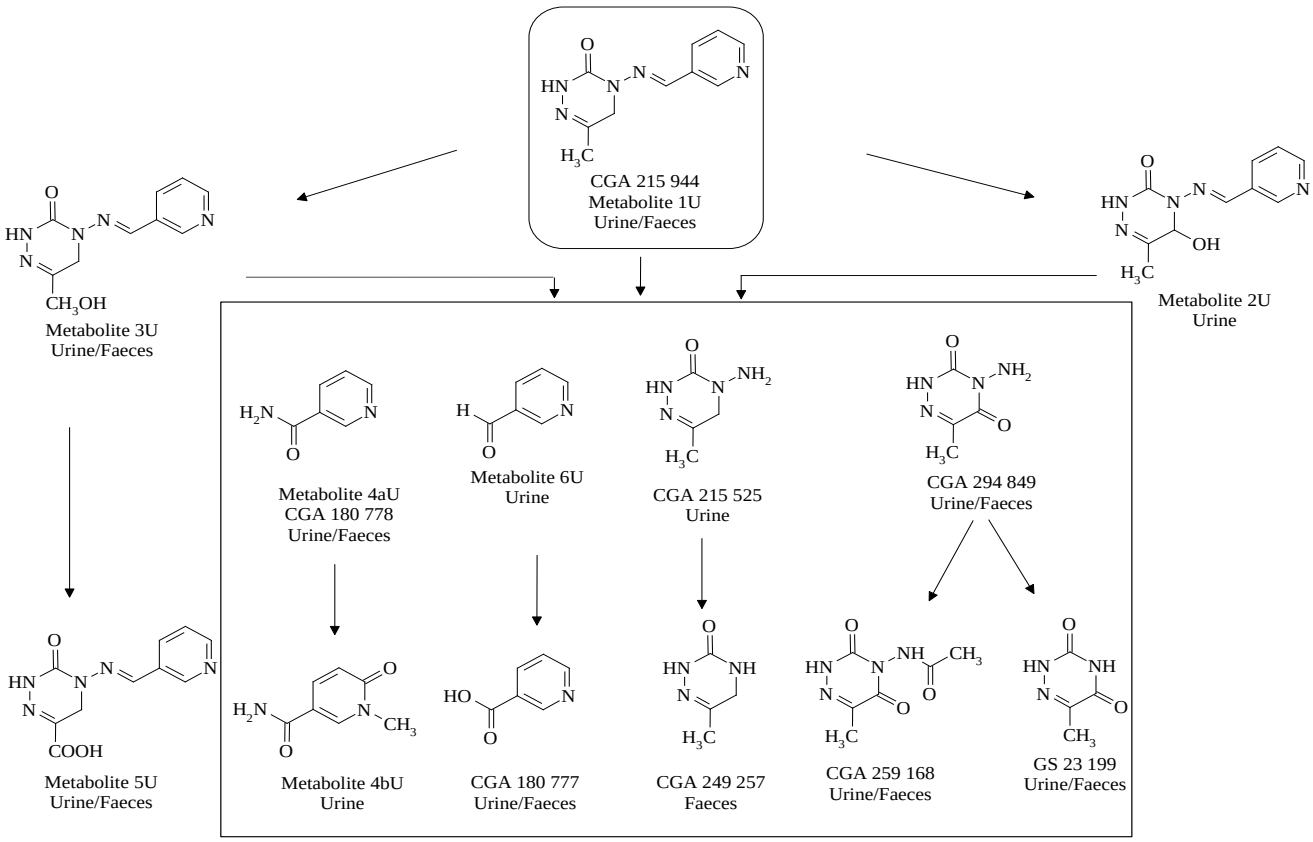
At the high dose, only the fat residues were proportionally higher. The data indicate a saturation of distribution and/or binding processes except on fat where the distribution of radioactivity was unhindered.

Pymetrozine was extensively metabolised and the metabolic pathways were independent of sex, pre-treatment and dose level. The derived metabolic pathways were oxidation reactions (about 19 % of the dose) at the methyl substitute leading to the corresponding carboxylic acid, oxidation reactions (about 7 % of the dose) at the triazine-methylene group leading to the corresponding alcohol, and cleavage reactions between the triazine and the pyridine ring systems (about 20 % of the dose).

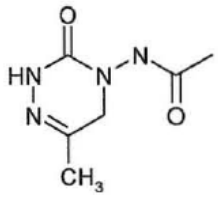
It is concluded that regardless of the dose level and the label position pymetrozine was well absorbed into the systemic circulation, from where it was eliminated in both urine and bile. Elimination from blood and tissues was biphasic. The proposed metabolic pathways in rats are depicted in Figure 1.

The major metabolic pathways proposed for rats are also valid for mice. The metabolic pathways are not influenced by pre-treatment with pymetrozine up to concentrations of 5000 ppm (mice) and 3000 ppm (rat).

Figure 1: Proposed metabolic pathways of pymetrozine in rats



According to a statement by industry (Hadfield, 2011 ASB2012-4624), the chemical structure of metabolite CGA259168 was incorrectly reproduced in the study reports and it would be a metabolite of CGA215525 (instead of metabolite CGA294849). According to the statement, the structure should have been given as:



10. EVALUATION OF HEALTH HAZARDS

This section contains short summaries taken from Vol. 1 (chapter 2.6) of the RAR, which was written for the pesticides procedure. In case more detailed information on the reported effects is needed, it is referred to the confidential annex to this document or Volume 3 / chapter B.6 of the RAR. The additional data/information submitted by industry during the preparation phase of this CLH dossier is also included and taken into account. All studies included in this dossier were evaluated and assessed by the dossier submitter.

10.1 Acute toxicity - oral route

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.2 Acute toxicity - dermal route

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.3 Acute toxicity - inhalation route

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.4 Skin corrosion/irritation

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.5 Serious eye damage/eye irritation

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.6 Respiratory sensitisation

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.7 Skin sensitisation

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.8 Germ cell mutagenicity

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.9 Carcinogenicity

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

Two long term toxicity and/or carcinogenicity studies were performed in mice and rats. The results are summarised in Table 12. Further details including method, guideline (and deviations if any), doses, substance purity (if known), species, strain, sex, no of animals/group, study duration, exposure route and a description of the results (including information on incidences and severities of findings and extent of changes relative to controls, etc.) are given in the text below or in the RAR.

Table 12: Summary of chronic toxicity/oncogenicity studies

Study	Dose levels	NO(A)EL	Target organs/main effects	Reference
18-months, mouse OECD TG 451 (1982)	0, 10, 100, 2000, 5000 ppm	100 ppm 11.4 mg/kg bw	Liver, spleen and lung toxicity, body weight reduced liver tumours in males at 2000 ppm and in both sexes at 5000 ppm lung tumours in females at 2000 ppm and in both sexes at 5000 ppm	(Author 3, 1995 TOX9652154)
24-months, rat OECD TG 453 (1982)	0, 10, 100, 1000, 3000 ppm	100 ppm 3.7 mg/kg bw	Liver toxicity, body weight reduced Benign hepatoma (f), malignant adrenal medullary tumour (m) at 3000 ppm	(Author 3, 1995 TOX9652155)

Under the conditions of the study, rats treated with 10 or 100 ppm (equal to 0.357/0.430 mg/kg bw/d or 3.73/4.45 mg/kg bw/d in males/females, respectively) showed no toxic findings throughout the study period. Animals treated with 1000 ppm (equal to 39.3/47.1 mg/kg bw/d) had lower body weights and feed intake. Relative liver, kidney and spleen weights of males were increased at interim sacrifice (but not at terminal sacrifice). Microscopic analysis revealed hepatocellular hypertrophy and thyroid follicular epithelium hyperplasia. At the next higher dose level of 3000 ppm (equal to 128/154 mg/kg bw/d) the following additional findings were observed: lower red blood cell count in week 13, changes in several clinical chemistry parameters (plasma glucose, chloride, albumin, bilirubin, cholesterol, inorganic phosphorous), increased relative liver, kidney and spleen weights in both sexes at interim and terminal sacrifice. Several macroscopic and histopathological findings were observed in liver (cysts, masses, mottled appearance, hypertrophy, foci of change, benign hepatoma), thyroid (follicular epithelium hyperplasia), uterus (dilatation) and adrenals (medullary tumours).

Table 13: Selected incidences of neoplastic microscopic lesions in rats (including data from the animals of the interim sacrifice)

Sex	Males					Females				
Feeding level, ppm	0	10	100	1000	3000	0	10	100	1000	3000
Liver / Total examined	60	60	60	60	60	60	60	60	59	60
Benign hepatoma +)	2 (3 %)	0	2 (3 %)	0	2 (3 %)	0	0	0	2(3 %)	7 (12 %)***
Adrenal medulla / Total examined	60	60	60	60	60	60	60	60	60	60
Benign medullary tumor	2	0	3	2	1	0	1	0	0	1
Malignant medullary tumor ++)	0	0	1	0	3 (5 %)	0	0	0	0	0
Cereb. meninges / Total examined	60	60	60	60	60	60	60	60	60	60
Benign gran. cell tumor +++)	0	0	0	1	2* (3 %)	1	0	1	0	1

Peto-Test: * = p<0.05; *** = p<0.0001

+) Historical control incidence in females: 0 - 3 % in the conducting laboratory between 1989 & 1993, up to 8 % according to Registry of Industrial Toxicology Animal-data, Hannover, Germany

++) Historical control incidence in males: 0 - 3 % for malignant medullary tumor and 4 - 12 % for benign & malignant medullary tumor in the conducting laboratory between 1989 & 1993.

+++) Historical control incidence in males: 0 - 5 % in the conducting laboratory between 1989 & 1993.

Under the conditions of the 18-month study in mice, no adverse effects were reported in groups treated with dietary dose levels of 10 or 100 ppm (equal to 1.24/1.17 or 12.0/11.4 mg/kg bw, respectively, males/females). In animals treated with 2000 ppm (equal to 254/243 mg/kg bw/d), body weight gain was reduced and organ weights of liver, kidney and adrenals were changed. Macroscopic and microscopic findings were observed in liver (masses in males, enlarged organ, hypertrophy and tumours), spleen (enlarged, extramedullary haematopoiesis, haemosiderosis), lung (nodules, tumours above historical control range) and bone marrow (hypercellularity). At the next higher dose level of 5000 ppm (equal to 678/673 mg/kg bw/d), survival of males was increased and feed intake was reduced. Haematology parameters related to red blood cells were reduced. Following additional macroscopic and microscopic findings were observed in liver (nodules, mottled appearance, necrosis) and stomach (inflammation, hyperplasia).

Table 14: Selected incidences of neoplastic microscopic lesions in mice

Sex	**Males**					**Females**				
Feeding level, ppm	0	10	100	2000	5000	0	10	100	2000	5000
Liver / Total examined	50	50	50	49	50	49	50	50	50	50
Benign hepatoma	10	3	12	9	11 (22 %)	4	5	4	1	14* (28 %)
Carcinoma	5	5	5	9** (18 %)	23** (46 %)	0	0	0	0	4** (8 %)
Hepatoma + Carcinoma	15	8	17	18	34** (68 %)	4	5	4	1	18** (36 %)
Lung / Total examined	50	49	49	50	50	49	50	50	50	50
Adenoma +	14	8	11	14	13	6	3	3	9 (18 %)	8 (16 %)
Carcinoma ++	1	1	3	1	0	1	1	5 (10 %)	7 (14 %)	2
Adenoma + Carcinoma +++	15	9	14	15	13	7	4	8	16* (32 %)	10* (20 %)

Peto-Test: * = $p<0.05$; ** = $p<0.001$

+) Historical control incidence in females: 3 - 13 % in the conducting laboratory between 1988 & 1991

++) Historical control incidence in females: 2 - 7 % in the conducting laboratory between 1988 & 1991

+++) Historical control incidence in females: 5 - 18 % in the conducting laboratory between 1988 & 1991

No human data on carcinogenicity are available.

Special mechanistic studies elucidating the formation of liver tumours were conducted in mice and rats.

Subchronic studies on selected biochemical and morphological liver parameters in male mice (Author 8 & Author 5, 1995) showed that pymetrozine was a moderate and largely reversible inducer of foreign compound metabolising liver enzymes and that proliferation of smooth endoplasmatic reticulum (SER) in the liver was stimulated. Based on the specific induction of cytochrome P450 isoenzyme of the gene family CYP3A in the mouse, pymetrozine was addressed as a pregnenolone-16α-carbonitrile-type inducer. The feeding level of 500 ppm was a NOEL in this study.

Liver cell proliferation was studied in male mice administered pymetrozine for up to 42 days (Author 5, 1995). The results demonstrated that, at 2000 and 5000 ppm, the test article induced a sustained but reversible stimulation of hepatocyte cell proliferation and that the observed hepatomegaly in the mouse liver at these high dose levels was the result of hypertrophy and hyperplasia. The 500 ppm feeding level represented a NOEL for this effect.

It was concluded that the reversible biochemical and morphological changes in these studies correlated with mice liver tumours observed in the chronic mouse study at the same dose levels.

A subchronic feeding study in female rats (Author 1, 1996) on selected biochemical and morphological liver parameters and on replicative DNA synthesis in hepatocytes showed that pymetrozine is a weak and

reversible inducer of xenobiotic metabolising enzymes, most prominent on glucuronosyl transferase at 1000 and 3000 ppm. Proliferation of smooth endoplasmatic reticulum membranes was observed only at the top dose of 3000 ppm.

The analysis of thyroid hormones indicated a slight stimulation of the thyroid gland by pymetrozine.

The feeding level of 100 ppm was a NOEL in this study. Pymetrozine had no measurable effect on hepatocyte proliferation under the conditions of this study, possibly due to the relatively short duration of administration.

It was concluded that the reversible biochemical and morphological changes in this study correlated with the slight increase in benign liver tumours observed in females in the chronic rat study at the same dose level.

Pymetrozine did not exhibit a tumour promoting potential in liver up to the highest dose level tested of 1000 ppm, but possessed weak promoting activity for the thyroid carcinogenesis at 100 and 1000 ppm under the experimental conditions of a liver and thyroid medium-term bioassay system in rats (Author 7, 1996).

10.9.2 Comparison with the CLP criteria

Table 15 presents the CLP criteria for classification as a carcinogen.

Table 15: Criteria for classification

CLP regulation
A substance is classified in Category 1 (known or presumed human carcinogens) for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as: Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence. The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from: — human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or — animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals. The placing of a substance in Category 2 (suspected human carcinogens) is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited (1) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies. […] 3.6.2.2.3. Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the substance and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms ‘sufficient’ and ‘limited’ have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows: (a) Carcinogenicity in humans The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories: — sufficient evidence of carcinogenicity: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence; — limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence. (b) Carcinogenicity in experimental animals Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals. The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories: — sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites; — limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

CLP regulation
3.6.2.2.4. Additional considerations (as part of the weight of evidence approach (see 1.1.1)). Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans. The full list of factors that influence this determination would be very lengthy, but some of the more important ones are considered here. 3.6.2.2.5. The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner. 3.6.2.2.6. Some important factors which may be taken into consideration, when assessing the overall level of concern are: (a) tumour type and background incidence; (b) multi-site responses; (c) progression of lesions to malignancy; (d) reduced tumour latency; (e) whether responses are in single or both sexes; (f) whether responses are in a single species or several species; (g) structural similarity to a substance(s) for which there is good evidence of carcinogenicity; (h) routes of exposure; (i) comparison of absorption, distribution, metabolism and excretion between test animals and humans; (j) the possibility of a confounding effect of excessive toxicity at test doses; (k) mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity. Mutagenicity: it is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity *in vivo* may indicate that a substance has a potential for carcinogenic effects.

There are no relevant data from epidemiological studies submitted by Syngeta, hence no classification with Cat. 1A according to CLP regulation is proposed.

Long-term dietary toxicity studies were conducted in rats and mice.

In mice treated for 18 month with pymetrozine, males (treated with 2000 or 5000 ppm) and females (treated with 5000 ppm) showed higher incidences in liver carcinoma and at the higher doses level the incidence of combined liver benign hepatoma and carcinoma was increased in males and females. In females (treated with 2000 or 5000 ppm) higher incidences in lung adenoma and the combined incidence of lung „adenoma + carcinoma“ were observed. Lung carcinoma in females were also increased at 100 and 2000 ppm, however the dose-response was less clear. The tumours in lung and liver were corroborated by masses or nodules observed in these organs.

Pymetrozine induced metabolising enzymes (CYP3A) and proliferation of smooth endoplasmatic reticulum in livers of treated mice. Reversible stimulation of hepatocyte cell proliferation and hepatomegaly in the mouse liver were observed.

In livers of animals treated for 90 days with different dietary doses of pymetrozine, several histological liver changes (organ weight increase, hypertrophy, necrosis, aggregates of lymphocytes) were noted in males and females. No treatment-related histological findings were reported in lungs in this subchronic study.

In rats treated for 2 years with pymetrozine, increased incidences of tumours were observed in top dose (3000 ppm). In males, a significant higher incidence of malignant adrenal medullary tumours was observed (outside the historical control range of the laboratory), although the combined incidence of benign and malignant adrenal medullary tumours was not significantly increased. In females, benign liver hepatoma were significantly increased (outside the historical control range of the laboratory). The incidence of benign granular cell tumours in cerebral meninges of males was also increased but within the historical control range of the laboratory. Findings in liver were corroborated by foci of cellular change in both sexes.

Pymetrozine induced metabolising enzymes (most prominent on glucuronosyl transferase) and proliferation of smooth endoplasmatic reticulum in livers of treated rats. No effect on hepatocyte proliferation was

observed. Pymetrozine did not exhibit a tumour promoting potential for the liver up to the highest dose tested of 1000 ppm, but possessed weak promoting activity for the thyroid carcinogenesis at 100 and 1000 ppm under the experimental conditions using a liver and thyroid medium-term bioassay system in rats. (However, thyroid tumours were not observed in the rat carcinogenicity study.)

According to literature[1] on adrenals findings, „most studies have reported a higher incidence [of pheochromocytomas] in males than in females. […] Both spontaneous and xenobiotic induced pheochromocytomas are less common in the mouse". Further on[2], „pheochromocytoma is a commonly observed tumor in aged rats, particularly in males. Tumors rarely occur before one year of age and the incidence increases thereafter." Hence, it is not unusual, that medullary tumours were observed in males only. Neither in subchronic nor in chronic studies in rats, indications were reported for adverse effects on adrenals. In contrast to this, liver was the target organ in subacute, subchronic and chronic studies in rats.

Taken together, oral administration was used in the studies which is a relevant exposure pathway. The compound was not genotoxic/mutagenic *in vitro* and *in vivo* in the available studies. Neither multi-site response nor reduced tumour latency were reported. For certain combinations of tumour type and dose level either one or both sexes were affected. Only up to a certain extent a consistent pattern of carcinogenicity regarding affected sex or species can be concluded from the available results of the submitted studies. Liver tumours - however of different types – were observed in two species. No ADME data in humans are available; therefore, no comparison is possible with the respective animal data. Body weight in top dose groups in mice and rats were quite low when compared to the respective control groups. No reduction of survival rates was reported.

The available mechanistic data do not explain the occurrence of the observed tumours or the mode of action of their induction. Therefore, it is not possible to analyse the relevance of the observed tumours with the "IPCS framework for analysing the relevance of a cancer mode of action for humans"[3] ("postulate mode of action" would be the first step of the framework). No data are available to show that the tumours observed in experimental animals are not relevant to humans.

Pymetrozine is currently listed in Table 3.1 in CLP regulation with H351.

No "sufficient evidence of carcinogenicity" can be demonstrated when considering the strengths and weaknesses of the available studies and their results. Hence no classification with category 1B according to CLP regulation is proposed.

When balancing the factors for increasing or decreasing the level of concern, and deciding whether there is a "limited evidence of carcinogenicity", it is proposed to keep the classification of pymetrozine for carcinogenic properties (category 2 (H351)).

The CoRMS of the pesticides procedure (Belgium) indicated that hepatic tumours observed in rats and mice and a MoA potentially relevant for humans (stimulation of hepatocyte cell division), might be a reason to trigger higher classification for carcinogenicity.

During the pesticides peer-review procedure it was not discussed, whether there is a need to change the existing harmonised classification.

[1] Rosol et al. (2001): Adrenal gland: structure, function, and mechanism of toxicity, Toxicologic Pathology 29(1):41-48

[2] Paterson et al. (1995): Proliferative lesions of the adrenal glands in rats, in: Guides for toxicologic pathology; available under: http://www.toxpath.org/ssdnc/AdrenalProliferativeRat.pdf [link checked on August 7, 2014]

[3] Boobis et al. (2006): IPCS Framework for Analyzing the Relevance of a Cancer Mode of Action for Humans, Critical Reviews in Toxicology, 36:781–792

10.9.3 Conclusion on classification and labelling for carcinogenicity

In summary, classification in Category 2 (H351) is considered appropriate.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

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

The reproductive toxicity of pymetrozine was assessed in a multi-generation study in rats. The results of this study are summarised in Table 16. Further details including method, guideline (and deviations if any), doses, substance purity (if known), species, strain, sex, no of animals/group, study duration, exposure route and a description of the results (including information on incidences and severities of findings and extent of changes relative to controls, etc.) are given in the text below or in the RAR.

In the 2-generation study the highest dose level was toxic for both parents and offspring. The parental and offspring body weights were reduced, eye opening was slightly delayed in pups, and histopathology of adults revealed changes in liver, spleen, and the pituitary. No effects on reproduction or fertility were reported up to the highest dose tested.

Histological findings in gonads and (slight) changes in hormone levels were reported in repeated-dose toxicity studies in rats and dogs (Table 17).

No human data on adverse effects on sexual function and fertility are available.

Table 16: Summary of reproductive toxicity studies

Study	Dose levels	NO(A)EL	Target organs/main effects	Reference
2-generation study in rats OECD TG 416 (1983)	0, 20, 200, 2000 ppm	<u>parents & offspring:</u> 200 ppm (13.92/15.98 mg/kg bw/d) <u>reproduction:</u> 2000 ppm (126.9/151.6 mg/kg bw/d)	reduced bw at 2000 ppm in parents and offspring; target organs: liver, spleen, pituitary; delayed development in pups no effects on reproduction or fertility	(Author 2, 1993 TOX9652156)

Comparison with the CLP criteria

Table 17: Toxicological results concerning adverse effects on sexual function and fertility

Toxicological result	CLP criteria
2-generation reproduction study in rats, pymetrozine administered via diet (Author 2, 1993 TOX9652156): No effects on fertility or reproduction observed up to highest dose tested (2000 ppm, 126.9/151.6 mg/kg bw/d)	Category 1A: Known human reproductive toxicant Category 1B: Presumed human reproductive toxicant largely based on data from animal studies - clear evidence of an adverse effect on sexual function and fertility in the absence of other toxic effects, or - the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects Category 2: Suspected human reproductive toxicant - some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility and - where the evidence is not sufficiently convincing to place the substance in Category 1 (deficiencies in the study). - the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects
28-d studies in rats: 600 mg/kg bw/d (1992 ASB2012-4619): reduced spermatogenesis in testes, reduced spermatozoa in epididymis 162.8 mg/kg bw/d (3000 ppm) (Author 4, 1998 TOX9851465; Author 4, 1998 TOX9851464): rounded spermatids 691 mg/kg bw/d (10000 ppm) (Author 3, 1991 TOX9652142): reduced spermatozoa in epididymis 254.7 mg/kg bw/d (5000 ppm) (Author 4, 1998 TOX9851465; Author 4, 1998 TOX9851464): hormone changes (testosterone, dihydrotestosterone, luteinising hormone, T4), testes (weight increase; in one animal: unilateral atrophy of testis & seminiferous tubular atrophy) and affected spermatogenesis (preleptotene & pachytene spermatocytes decreased) **28-d studies in dogs:** ~ 50 mg/kg bw/d (2500 ppm) (1991 TOX9652143): no relevant findings up to highest dose tested 61 mg/kg bw/d (2000 ppm) (Author 4, 1998 TOX9851466): low dihydrotestosterone levels, testes (histological findings in one animal: giant cell formation, decrease of sperm, degenerated spematogenic cells) **90-d (tox) studies in rats & mice:** No relevant findings up to highest dose tested (~360 or ~1000 mg/kg bw/d, respectively) **90-d study in dogs:** 14 mg/kg bw/d (500 ppm) (1992	

Toxicological result	CLP criteria
TOX9652145; 1992 ASB2012-4620; 1995 TOX9650867): tubular atrophy of testis, reduced spermatogenesis 53/60 mg/kg bw/d (2500 ppm): additionally, uterine atrophy **1-yr study in dogs:** 5 mg/kg bw/d (200 ppm) (1994 TOX9652153): testis (wt ↓) ~27 mg/kg bw/d (1000 ppm): unilateral tubular atrophy in one male, bilaterally spermatic giant cells in testicular spermatogenic epithelium **2-yr study in rats and 18-mo study in mice:** No relevant findings up to highest dose tested (~130 or ~670 mg/kg bw/d, respectively)	

In the submitted multigeneration study no findings with relevance for a classification for adverse effects on sexual function and fertility were reported.

Histological findings in testes accompanied by other toxic effects were observed in dogs and rats. The testes findings were most pronounced at the highest dose groups. However, some of the available studies have limitations in the group size or the set of parameters evaluated. Nevertheless, the evaluated parameters seemed to be assessed appropriately.

There are no epidemiological data to evaluate effects on fertility, hence pymetrozine cannot be placed in category 1A.

Overall, in several studies histological indications for adverse effects on fertility (spermatogenesis) were reported in low incidences, however, they were observed at dose levels inducing systemic toxicity[4]. Additionally, the findings observed in repeat-dose studies could not be corroborated in the 2-year study in rats or the multigeneration study in rats, however (slightly) lower dose levels were administered in the latter studies.

It seems that systemic effects of toxicity which were described in the study reports were not severe enough to induce non-specific findings in testes and to render the observed histological findings as non-specific and non-relevant findings for classification. No data are available to assess whether the testes effects in dogs might have an adverse impact on mating success.

It should be noted, that the rat (multigeneration study) is a limited / poor model to assess certain adverse effects on fertility, because an impact on fertility rate in rats is observed only after severe reductions of

[4] ECHA: Guidance on the application of the CLP criteria, Version 3.0 November 2012 (Section 3.7.2.2.1.1, p. 324): „Adverse effects on fertility and reproductive performance seen only at dose levels causing marked systemic toxicity (e.g. lethality, dramatic reduction in absolute body weight, coma) are not relevant for classification purposes.

There is no established relationship between fertility effects and less marked systemic toxicity. Therefore it should be assumed that effects on fertility seen at dose levels causing less marked systemic toxicity are not a secondary consequence of this toxicity."

sperm numbers (e.g., Working, 1988[5]), whereas in humans fertility rate is reduced already by less extensive reductions in sperm numbers. The value and relevance of histological evaluation of testes is also emphasised in the OECD test guideline 443 and some RAC opinions on harmonised classification of chemicals.

Taking into account the relatively low incidences which were observed in several studies, DS sees "some evidence" but not a "clear evidence" for adverse effects on reproduction and therefore, proposes a classification with category 2 (H361f).

10.10.2 Adverse effects on development

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

The reproductive toxicity of pymetrozine was assessed in two teratology studies in rats and rabbits. After the PPP procedure, DS was informed that EPA had evaluated a developmental neurotoxicity (DNT) study with pymetrozine in rats. During preparation phase of the current CLH dossier this study was provided by Syngenta and evaluated by the DS.

The results of these studies are summarised in Table 18. Further details including method, guideline (and deviations if any), doses, substance purity (if known), species, strain, sex, no of animals/group, study duration, exposure route and a description of the results (including information on incidences and severities of findings and extent of changes relative to controls, etc.) are given in the text below or in the RAR.

The two teratology studies in rats and rabbits revealed developmental changes at dose levels at which maternal toxicity was also apparent.

Under the conditions of the rat developmental toxicity study, slight maternal toxicity was reported at dose levels of 300 and 100 mg/kg bw/d (reduced feed intake and body weight (gain)). At animals dosed with 300 mg/kg bw/d, four foetuses in three litters with displaced pubic bones (classified by the study director as malformation) and several foetuses with anomalies or variations were observed. At a dose level of 100 mg/kg bw/d, an increased incidence of variations (dumbbell-shaped cervical vertebral centres) was observed. No effects were observed in animals treated with 30 mg/kg bw/d. The NOAEL for maternal and developmental effects was at 30 mg/kg bw/d.

In the study report the pelvic findings reported at 300 mg/kg bw/d were described as follows:

- Female 75 / Foetus 15: Displaced pubis; present; left. Left pubic bone displaced parasagittally and rotated ca. 60 deg.
- Female 79 / Foetus 3: Displaced pubis; present; left. Left pubic bone displaced parasagittally and rotated ca. 30 deg.
- Female 80 / Foetus 9: Displaced pubis; present; bilateral. Both pubic bones displaced parasagittally and rotated ca. 30 deg.
- Female 80 / Foetus 13: Displaced pubis; present; bilateral. Both pubic bones displaced parasagittally and rotated ca. 30 deg.

Under the conditions of the rabbit developmental toxicity study, administration of 125 and 75 mg/kg bw/d of the test compound induced toxicity in does (mortality, reduced feed intake and body weight gain). In foetuses of these dose levels, external and skeletal examination revealed several findings (altered position of forelimb, fused sternebrae, reduced pubis, poor ossification of several bones and occurrence of 13th rib). The NOAEL for developmental and maternal effects was 10 mg/kg bw/d.

[5] Working (1988): Male reproductive toxicology: comparison of the human to animal models, Environmental health perspectives 77, 37-44

In the study report the reduced pubis reported at 75 mg/kg bw/d (females 44 and 53) and 125 mg/kg bw/d (females 66 and 73) were described as follows:

- Female 44 / Foetus 4: Reduced pubis; present; bilateral.
- Female 53 / Foetus 6: Reduced pubis; present; bilateral.
- Female 66 / Foetus 3: Reduced pubis; present; bilateral.
- Female 73 / Foetus 5: Reduced pubis; present; right.
- Female 73 / Foetus 6: Reduced pubis; present; right.

It is important to note that changes in the pelvis occurred in both species. Interestingly, defects of this kind have not been recorded in historic controls in rabbits and only in low incidences in rats.

In the DNT study only two dose groups were evaluated: Due to excessive maternal toxicity (body weight loss, lower feed consumption, clinical signs) and high pup mortality the highest dose group of 2500 ppm was terminated before schedule. At the mid dose level of 500 ppm decreased body weight gain of ca 10 % was reported in dams but did not gain statistical significance, therefore this finding was considered not adverse. When compared to multi-generation study, the high level of maternal toxicity at the top dose is noted.

Changes in brain morphometry in F1 animals were observed in all evaluable dose groups starting at the lowest dose group of 100 ppm (equal to 8.1 mg/kg bw per day). Neonatal mortality including complete litter losses was reported at 500 ppm (equal to 38.7 mg/kg bw per day). No further effects on development, neurological or behavioural parameters were observed based on the information given in the study report.

No human data on adverse effects on development are available.

Table 18: Summary of developmental toxicity studies

Study	Dose levels	NO(A)EL	Target organs/main effects	Reference
Teratology study, rat OECD TG 414 (1981)	0, 30, 100, 300 mg/kg	maternal: 30 mg/kg foetal: 30 mg/kg	maternal toxicity and developmental changes (pelvis, delayed ossification) at 100 and 300 mg/kg	(Author 2, 1992 ASB2012-4617)
Teratology study, rabbit OECD TG 414 (1981)	0, 10, 75, 125 mg/kg	maternal: 10 mg/kg foetal: 10 m/kg	maternal toxicity, embryotoxicity, foetotoxicity and developmental changes (pelvis, fused sternebrae, delayed ossification) at 75 and 125 mg/kg	(Author 2, 1992 ASB2012-4618)
Developmental neurotoxicity study in rats US EPA OPPTS 870.6300 (1998)	0, 100, 500 ppm, 2500 ppm 0, 8.1, 38.7, 173.1 mg/kg bw/d	maternal: 500 ppm (38.7 mg/kg bw/d) foetal: < 100 ppm (8.1 mg/kg bw/d	At 2500 ppm termination due to severe maternal and pup toxicity. At 500 ppm non-significant decreased maternal body weight gain, reduced feed consumption post partum d 1-5 without influence on body weight post partum and possibly related to cannibalism. At 100 ppm and above brain morphometry changes at PND 12 and 63. At 500 ppm increased pup mortality PND 1 – 5	(Author 6, 2003 ASB2015-3677)

Comparison with the CLP criteria

Table 19: Toxiclogical results concerning adverse effects on development

Toxicological result	CLP criteria
Teratology study in rats (Author 2, 1992 ASB2012-4617): Displaced pubis bones, thickened ischium of pelvis, asymmetrically shaped sternebrae and poor ossification in several digit bones at 300 mg/kg bw/d Lower body weight gain and feed intake at 100 and 300 mg/kg bw/d	Category 1A: Known human reproductive toxicant Category 1B: Presumed human reproductive toxicant largely based on data from animal studies - clear evidence of an adverse effect on development in the absence of other toxic effects, or - the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects Category 2: Suspected human reproductive toxicant - some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on development and - the evidence is not sufficiently convincing to place the substance in Category 1 (deficiencies in the study). - the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects
Developmental neurotoxicity study in rats (Author 6, 2003 ASB2015-3677): Brain morphometry changes in all dose groups from 8.1 mg/kg bw per day Pup mortality on PND 1-5 at 38.7 mg/kg bw per day severe maternal and pup toxicity at 173.1 mg/kg bw per day	
Teratogenicity study in rabbits (Author 2, 1992 ASB2012-4618): Post implantation loss, reduced pubis at 75 and 125 mg/kg bw/d Fused sternebrae and several variations at 125 mg/kg bw/d 2 dams died in 125 mg /kg bw/d dose group (GD 16 and 19), one was sacrificed in control group (GD 16) Slight body weight loss in top dose group and lower body weight gain in mid dose group during treatment period	

There are no appropriate epidemiological studies available on developmental effects in humans. Hence, classification with Category 1A according to CLP regulation is not possible.

The prenatal developmental toxicity was investigated in rats and rabbits and a developmental neurotoxicity study in rats complying to international test guidelines and GLP.

In rats, findings in offspring included displaced pubic bones (classified by the study director as malformation) and several foetuses with anomalies or variations in the top dose group. In mid dose group, increased incidence of variations (dumbbell shaped cervical vertebral centres) was observed. At the same dose levels, reduced feed intake and body weight (gain) were observed in dams.

In rabbits, altered position of forelimb, fused sternebrae, reduced pubis, poor ossification of several bones and occurrence of 13th rib were observed in offspring in top and mid dose group. In does, lower body weight gain was observed during the treatment period in mid dose group and body weight loss during the treatment period and mortality were observed in top dose group.

According to the website "www.devtox.org", the findings "small pubis" (incompletely developed structure, or less than normal in size), "malpositioned pubis" (not occurring in the proper position and/or orientation) and "misshapen pubis" (abnormally shaped [Not to be used to describe sites of incomplete ossification]) are considered malformations. Whereas, the finding "misaligned pubis" (abnormal relative position of structures on opposite sides of a dividing line or about the centres or axis) is not considered a malformation.

In addition to the data presented above and in the confidential annex, no further data/information is included in the study reports, which would allow judging the functional impact of the pubis dysplasia. However, changes in pubis alignment or position may affect posture, gait and can cause pain. Hence, in humans, such diagnoses are considered malformations if they are induced during pregnancy, or can lead to severe disability if they are acquired later on.

While the standard reference point for the evaluation of treatment responses shall be concurrent control data, historical control data may be helpful in the interpretation of particular developmental studies. Where submitted, historical control data shall be from the same species and strain, maintained under similar conditions in the same laboratory and shall be from contemporaneous studies (adapted from regulation (EU) No 283/2013).

The Guidance on the Application of the CLP Criteria (Version 4.1, June 2015, section 3.6.2.3.2., p. 376) explains only the use of historical control data regarding the evaluation of tumour findings. But the general idea would by applicable to support the evaluation of malformations, too, *mutatis mutandis*:

> *"Use of historical control data should be on a case by case basis with due consideration of the appropriateness and relevance of the historical control data for the study under evaluation. In a general sense, the historical control data set should be matched as closely as possible to the study being evaluated. The historical data must be from the same animal strain/species, and ideally, be from the same laboratory to minimise any potential confounding due to variations in laboratory conditions, study conditions, animal suppliers, husbandry etc. It is also known that tumour incidences in control animals can change over time, due to factors such as genetic drift, changes in diagnostic criteria for pathological changes/tumour types, and husbandry factors (including the standard diet used), so the historical data should be contemporary to the study being evaluated (e.g. within a period of up to around 5 years of the study). Historical data older than this should be used with caution and acknowledgement of its lower relevance and reliability (RIVM, 2005; Fung et al, 1996; Greim et al, 2003)."*

It appears that the historical control data summarised by Author (1996) and Anon. (1997) (Tables B.6.6-13 and B.6.6-14 in the confidential annex or in the RAR) are from a relevant time period for a study conducted in 1991 (in-live phase).

In the available DNT study in rats, changes in brain morphometry were reported in the low dose group and above. Effects on brain morphometry in this study were also considered as adverse by US EPA. Additionally, higher neonatal mortality was observed in the mid dose group. Findings in low and mid dose groups were not accompanied by maternal toxicity.

Increased neonatal mortality was not reported in the multi-generation study in rats, despite the higher dose levels in the latter study.

Manifestations of developmental toxicity seen in developmental toxicity studies in rats and rabbits were accompanied by maternal toxicity. Abortion was observed in one (top dose) rabbits only. Several does had resorptions / post-implantation loss. Additionally, mortality was observed in top dose rabbits. Even though pubis was affected in rats and rabbits, dissimilar malformations were observed in the available studies.

The information from the DNT study in rats, which was received during preparation of this CLH dossier supports a classification as a developmental toxicant. Changes in brain morphometry were seen already in the low dose offspring. Additionally, higher neonatal mortality was observed in the mid dose group.

According to regulation (EC) No 1272/2008 major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth, and functional deficiency.

ECHA's Guidance on the application of the CLP criteria (Version 3.0 November 2012, Section 3.7.2.2.1.1, p. 325) cites the CLP regulation: "3.7.2.4.3 Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. …".

No information is available to confirm that the observed effects on offspring have to be regarded as secondary non-specific consequences of maternal toxicity. Additionally, according to the study report, findings in low and mid dose groups of the DNT study were not accompanied by maternal toxicity.

In summary, classification in Category 2 (H361d) is considered appropriate, also taking into account the limited increase in incidences in developmental toxicity studies. The CoRMS of the pesticides procedure (Belgium) indicated that pelvic effects observed in rats and rabbits, might be a reason to trigger higher classification for developmental toxicity.

10.10.3 Adverse effects on or via lactation

No data are available to judge whether there are specific effects on or via lactation (H362).

10.10.4 Conclusion on classification and labelling for reproductive toxicity

In summary, classification in Category 2 (H361fd) is considered appropriate.

10.11 Specific target organ toxicity-single exposure

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.12 Specific target organ toxicity-repeated exposure

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.13 Aspiration hazard

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

11. EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 ACUTE AQUATIC HAZARD

Table 20: Summary of relevant information on acute aquatic toxicity of pymetrozine

Method	Species	Test (endpoint, design, duration)	Results[1]	Key or Supportive study	Remarks	Reference
OECD 203	*Oncorhynchus mykiss*	Mortality static 96 hours	LC_{50} > 100 mg/L (nom)	key	none	Grade (1993); 928265
OECD 203	*Oncorhynchus mykiss*	Mortality flow-through 96 hours	LC_{50} > 128 mg/L (m)	supportive	none	Boeri (1994); 444-CG
OECD 203	*Cyprinus carpio*	Mortality static 96 hours	LC_{50} > 100 mg/L (nom)	supportive	None	Grade (1993); 928268
OECD 203	*Lepomis macrochirus*	Mortality static 96 hours	LC_{50} > 100 mg/L (nom)	supportive	None	Grade (1993); 928267
OECD 203	*Lepomis macrochirus*	Mortality flow-through 96 hours	LC_{50} > 134 mg/L (m)	supportive	none	Boeri (1994); 443-CG
OECD 203	*Ictalarus punctatus*	Mortality static 96 hours	LC_{50} > 100 mg/L (nom)	supportive	none	Grade (1993); 928266
OECD 203	*Cyprinodon variegatus*	Mortality flow-through 96 hours	LC_{50} > 117 mg/L (m)	supportive	none	Boeri (1994); 446-CG
OECD 202	*Daphnia magna*	Immobility static 48 hours	EC_{50} > 100 mg/L (nom)	supportive	none	Grade (1993); 928270
OECD 202	*Daphnia magna*	Immobility flow-through 48 hours	EC_{50} = 87 mg/L (m)	key	none	Boeri (1994); 442-CG
EPA 72-3	*Mysidopsis bahia*	flow-through 96 hours	EC_{50} = 61.7 mg/L (m)	supportive	none	Boeri (1994); 445-CG
EPA 72-3	*Crassostrea virginica*	Shell deposition flow-through 96 hours	EC_{50} = 3.06 mg/L (m)	key	none	Boeri (1994); 447-CG
OECD 201	*Scenedesmus subspicatus*	Growth inhibition Static 72 hours	EbC_{50} = 47.1 mg/L (m,end) ErC_{50} > 84.6 mg/L (m,end) NOErC = 7.5 mg/L (m)	key	none	Grade (1993); 928272
OECD 201	*Pseudokirchneriella subcapitata*	Growth inhibition Static 120 hours	EbC_{50} = 21.6 mg/L (m,initial) ErC_{50} > 96.7 mg/L (m,initial) NOErC = 6.28 mg/L (m)	key	none	Boeri (1994); 668-CG

[1] Indicate if the results are based on the measured or on the nominal concentration

11.1.1 Acute (short-term) toxicity to fish

The acute toxicity of pymetrozine (CGA 215944 tech.) to rainbow trout (*Oncorhynchus mykiss*), catfish (*Ictalarus punctatus*) , carp (*Cyprinus carpio*) and bluegill sunfish (*Lepomis macrochirus*) has been investigated by exposing fish under static conditions to concentrations between 0 and 100 mg/L of the test

substance followed by a 96 hours observation period. Up to 100 mg/L no mortalities occurred and no other symptoms were observed. Measured initial and final concentrations were between 91 % and 101 % for rainbow trout, 88 % and 104 % for catfish, 83 % and 92 % for carp and 83 and 103 % for bluegill sunfish of the nominal values.

The acute toxicity of pymetrozine (CGA 215944) to rainbow trout (*Oncorhynchus mykiss*), bluegill sunfish (*Lepomis macrochirus*) and sheepshead minnow (*Cyprinodon variegatus*) has been investigated by exposing fish under flow-through conditions. For rainbow trout up to concentrations of 128 mg/L no treatment related mortalities or effects were observed. Mean measured test concentrations were between 95 % and 104 % of the nominal values. For bluegill sunfish were no treatment related mortalities or effects reported up to concentrations of 134 mg/L. Mean measured test concentrations were between 91 % and 105 % of the nominal values. For the marine species sheepshead minnow were no treatment related mortalities or effects observed in a concentration range up to 117 mg/L. Mean measured test concentrations were between 88 % and 106 % of the nominal values.

Taking into account all acute studies for fish, where the lowest LC_{50} >100 mg/L was determined, no acute classification is necessary.

11.1.2 Acute (short-term) toxicity to aquatic invertebrates

In an acute static toxicity test with *Daphnia magna*, the 48-hour EC_{50} was determined to be > 100 mg pymetrozine (CGA 215944)/L, the highest concentration tested. The 48-hour NOEC was < 5.8 mg pymetrozine/L, the lowest concentration tested. At the start of the test, the measured concentrations of pymetrozine were in the range 79 to 98 % of the nominal values and at the end of the test were in the range 92 to 103 %. The limit of quantification for this study was not reported. Nominal concentrations were used for the calculation and reporting of results.

In a second study under flow through conditions with *Daphnia magna*, the 48-hour LC_{50} for pymetrozine was 87.0 mg pymetrozine (CGA 215944)/L with 95 % confidence interval of 67.9 – 131.0 mg pymetrozine /L. The 48-hour NOEC was < 19.2 mg pymetrozine /L, the lowest tested concentration. The mean measured concentrations of pymetrozine were in the range 92 to 99 % of the nominal values. The limit of detection in this study was 4.00 mg pymetrozine /L. The results were based on mean measured concentrations.

In another study under flow through conditions with *Mysidopsis bahia*, based on mean measured concentrations, the 96 hour LC_{50} was 61.7 mg pymetrozine /L, with 95 % confidence intervals of 52.4 to 73.1 mg pymetrozine /L. The 96-hour no-observed effect concentration (NOEC) was determined to < 18.7 mg pymetrozine /L, the lowest concentration tested. Mean measured concentrations ranged from 94 to 101 % of nominal values. The limit of detection in this study was 0.5 mg pymetrozine /L. Mean measured concentrations were used for the calculation and reporting of results.

Furthermore, in an acute toxicity test with the oyster *Crassostrea virginica*, the 96 hour EC_{50} was 3.06 mg pymetrozine /L, with 95 % confidence intervals of 2.13 to 4.38 mg pymetrozine /L. The 96-hour NOEC was determined to be 0.768 mg pymetrozine /L. Mean measured concentrations, calculated from the average of all samples, ranged from 94 to 112 % of nominal concentrations. Mean measured concentrations were used for the reporting of the results.

Taking into account all acute studies for invertebrates, where the lowest EC_{50} = 3.06 mg/L was determined, no acute classification is necessary.

11.1.3 Acute (short-term) toxicity to algae or other aquatic plants

The growth inhibition of algae (*Scenedesmus subspicatus*) by pymetrozine was studied in a static system at concentrations between 1.23 and 100 mg/L. The EbC_{50} and NOEbC after 3 days exposure were calculated to be 47.1 mg/L and 7.5 mg/L, respectively. These values are based on measured end concentrations, which

were after 3 days between 57 % and 86 % of the initial concentrations at the lowest and the highest dose level, respectively.

In a second study the toxicity of pymetrozine to the freshwater algae *Selenastrum capricornutum* was evaluated in a static system at concentrations between 6.3 and 100 mg/L. The ErC_{50} and NOErC after 5 days exposure were calculated to be 21.7 mg/L and 6.3 mg/L, respectively. These values are based on measured concentrations; analysis of the test medium showed recoveries between 93 and 100 % at the beginning but less than 70 % of the nominal values at the end of the test period.

Furthermore, the effect of pymetrozine on the growth of the duckweed *Lemna gibba* was studied for 14 days under static conditions at pH 5 and continuous illumination. Nominal test concentrations were 8.5 to 130 mg/L; the initial measured concentrations amounted to 71-84 % of the nominal concentrations (between 6.1 and 109 mg/L) but showed a strong decrease to below the analytical detection limit (5.1 mg/L) after 14 days, indicating some type of absorption or degradation. The EC_{25}, EC_{50} and NOEC values were 68, > 109 and 49 mg/L, respectively. They are determined on basis of effects on the frond production after 14 days exposure and refer to initial measured test concentrations. The NOEC is based on the number of non-chlorotic fronds.

Taking into account all acute studies for algae and aquatic plants, where the lowest ErC_{50} > 84.6 mg/L was determined, no acute classification is necessary.

11.1.4 Acute (short-term) toxicity to other aquatic organisms

No studies with other aquatic organisms in addition to the above mentioned are available.

11.2 LONG-TERM AQUATIC HAZARD

Table 21: Summary of relevant information on chronic aquatic toxicity of pymetrozine

Method	Species	Test (endpoint, design, duration)	Results	Key or Supportive study	Remarks	Reference
OECD 204	*Oncorhynchus mykiss*	growth Flow through 21 days	NOEC = 35.2 mg/L (m)	supportive	none	Grade (1993); 928269
EPA 72-4, OECD 210	*Oncorhynchus mykiss*	ELS Flow through 90 days (60 days post hatch)	NOEC = 11.7 mg/L (m)	key	none	Boeri et al (1995); 504-CG
OECD 202	*Daphnia magna*	Reproduction Semi static 21 days	NOEC = 0.1 mg/L (nom)	supportive	none	Grade (1993); 928271
EPA 72-4, OECD 202	*Daphnia magna*	Reproduction Flow through 21 days	NOEC = 0.025 mg/L (m)	key	none	Boeri et al (1995); 449-CG
OECD 201	*Pseudokirchneriella subcapitata*	Growth inhibition Static 120 hours	EbC_{50} = 21.6 mg/L (m,initial) ErC_{50} > 96.7 mg/L (m,initial) NOErC = 6.28 mg/L (m)	key	none	Boeri (1994); 668-CG
OECD 201	*Scenedesmus subspicatus*	Growth inhibition Static 72 hours	EbC_{50} = 47.1 mg/L (m,end) ErC_{50} > 84.6 mg/L (m,end) NOErC = 7.5 mg/L (m)	key	none	Grade (1993); 928272
EPA 122-2	*Lemna gibba*	Frond number Static 14 days	EC_{50} > 109 mg/L (m,initial) NOEC = 49.2 mg/L (m,initial)	supportive	none	Boeri et al (1995); 669-CG

[1] Indicate if the results are based on the measured or on the nominal concentration

11.2.1 Chronic toxicity to fish

In a first study the chronic toxicity of pymetrozine to rainbow trout has been investigated by exposing fish under flow through conditions for 21 days to pymetrozine concentrations between 0 and 100 mg/L. No mortalities occurred; at the highest applied concentration (120 mg/L, mean measured), however, the rates of weight gain and of length increase were decreased. No other treatment related symptoms were observed. Thus, the LC_{50} was > 120 mg/L, the LOEC and NOEC values are characterized by values of 120 mg/L and 35.2 mg/L, respectively.

As a second study in a fish early life stage test with pymetrozine, egg hatching success was unaffected at all concentrations of pymetrozine tested. No other sub-lethal effects were noted in any test vessel during the test, and the times to hatch, swim up and feeding (day 41) were identical for the controls and all treatments. The NOEC was 11.7 mg pymetrozine /L, the highest concentration tested.

11.2.2 Chronic toxicity to aquatic invertebrates

In a first semi static reproduction test with *Daphnia magna*, the 21-day EC_{50} immobilisation for pymetrozine was 0.6 mg pymetrozine /L, based on nominal concentrations. The 21-day NOEC for reproduction was 0.1 mg pymetrozine /L. The measured concentrations of pymetrozine in the new test media were in the range 63

to 98 % of the nominal values and the measured concentrations in the old media were in the range 72 to 143 %. Nominal concentrations were used for the calculation and reporting of the results.

In a second reproduction test with *Daphnia magna* under flow through conditions, the 21-day LC_{50} for pymetrozine was 0.0735 mg pymetrozine /L with 95 % confidence interval of 0.064 to 0.0847 mg pymetrozine /L, based on mean measured concentrations. The 21-day NOEC reproduction was 0.0251 mg pymetrozine /L. The measured concentration of the test item in the test media were in the range 78 to 94 % of the nominal values and concentrations were stable during the test. Measured concentrations were used for the calculation and reporting of the results. Survival of the parent animals was 98 % in the control. Survival in the 0.0251, 0.0515, 0.102, 0.234 and 0.462 mg pymetrozine /L treatment groups was 98, 80, 25, 0 and 0 %, respectively, at test termination.
The first brood juveniles were observed on day 9 in the control. The mean time to first brood was significantly different from the control at ≥ 0.102 mg pymetrozine /L. The mean number of juveniles per surviving adult showed a statistically significant inhibitory effect on the reproduction of *D. magna* over 21 days at concentrations of 0.0515 mg pymetrozine /L and above.

Taking into account all long term studies for invertebrates, where the lowest NOEC= 0.0251 mg/L was determined, a long term classification is necessary.

11.2.3 Chronic toxicity to algae or other aquatic plants

The growth inhibition of algae (*Scenedesmus subspicatus*) by pymetrozine was studied in a static system at concentrations between 1.23 and 100 mg/L. The EbC50 and NOEbC after 3 days exposure were calculated to be 47.1 mg/L and 7.5 mg/L, respectively. These values are based on measured end concentrations, which were after 3 days between 57 % and 86 % of the initial concentrations at the lowest and the highest dose level, respectively.

In a second study the toxicity of pymetrozine to the freshwater algae *Selenastrum capricornutum* was evaluated in a static system at concentrations between 6.3 and 100 mg/L. The ErC50 and NOErC after 5 days exposure were calculated to be 21.7 mg/L and 6.3 mg/L, respectively. These values are based on measured concentrations; analysis of the test medium showed recoveries between 93 and 100 % at the beginning but less than 70 % of the nominal values at the end of the test period.

Furthermore, the effect of pymetrozine on the growth of the duckweed *Lemna gibba* was studied for 14 days under static conditions at pH 5 and continuous illumination. Nominal test concentrations were 8.5 to 130 mg/L; the initial measured concentrations amounted to 71-84 % of the nominal concentrations (between 6.1 and 109 mg/L) but showed a strong decrease to below the analytical detection limit (5.1 mg/L) after 14 days, indicating some type of absorption or degradation. The EC_{25}, EC_{50} and NOEC values were 68, > 109 and 49 mg/L, respectively. They are determined on basis of effects on the frond production after 14 days exposure and refer to initial measured test concentrations. The NOEC is based on the number of non-chlorotic fronds.

11.2.4 Chronic toxicity to other aquatic organisms

No studies with other aquatic organisms in addition to the above mentioned are available.

11.3 BIOACCUMULATION

11.3.1 Estimated bioaccumulation

No estimation was performed for pymetrozine, because of log POW -0.19 at 25°C, pH 7.

11.3.2 Measured partition coefficient and bioaccumulation test data

Studies ascertaining the bioconcentration potential of pymetrozine were not conducted since the physico-chemical properties of pymetrozine (log POW -0.19 at 25°C, pH 7) and its more polar metabolites (log POW << 3) indicate that the inherent potential for bioconcentration is low.

11.4 RAPID DEGRADABILITY OF ORGANIC SUBSTANCES

Table 22: Summary of relevant information on rapid degradability

Method	Results	Key or Supportive study	Remarks	Reference
OECD 301 B	Not readily biodegradable (2% degradation within 29 days)	key	none	Grade, R. (1995)

11.4.1 Ready biodegradability

Pymetrozine has shown a biodegradation of 2 % in 29 days in a test according to OECD 301 B and has therefore to be regarded as not readily biodegradable.

11.4.2 BOD_5/COD

BOD5/COD tests are not available.

11.4.3 Other convincing scientific evidence

The behaviour of pymetrozine in two water/sediment-systems (Pond Fröschweiher, Rhine Möhlin) has been investigated in two studies with different radioactive labelling of the parent compound (Reischmann 1995a, Schulze-Aurich 1996b). The degradation rates have been recalculated in the study of Carnall & Ford (2011) following the latest FOCUS kinetic guidance.

A mineralisation of [triazinyl-6-14C]-labelled pymetrozine was measured with 25 % and 23 % AR after 361 days in the pond Fröschweiher and the Rhine river Möhlin systems, respectively. A comparable mineralisation was measured for the [pyridinyl-5-14C]-labelled pymetrozine with 29 % and 32 % AR after 344 days in the pond Fröschweiher and the Rhine river Möhlin systems, respectively.

43 % non-extractable residues of the [triazinyl-6-14C]-labelled pymetrozine were detected after 361 days in both water/sediment-systems, and 21-23 % non-extractable residues of the [pyridinyl-14C]-labelled pymetrozine were detected after 344 days in the pond Fröschweiher and the Rhine river Möhlin systems, respectively.

The degradation rates of the different labelled active substance pymetrozine in the two water-sediment systems have been recalculated in the study of Carnall & Ford (2011) following the latest FOCUS kinetic guidance. The resulting half-lives are summarised in table below. Pymetrozine dissipated with normalised half-lives (recalculated SFO from FOMC-DT90/3.32) between 7.4 and 13.1 days from the water phase. For the sediment phase SFO half-lives between 265 and 425 days were calculated. Normalised DegT50 values (recalculated SFO from DFOP kslow) between 315 and 495 days were calculated for the total water/sediment systems. Geometric mean DT50 values from the different pymetrozine labelling were calculated by the RMS for the water and sediment compartments and the total systems of each water/sediment system. Finally, overall geometric mean DT50 values of 9.5 days, 312 days and 358 days were derived for the water phase, sediment phase and the total systems, respectively and may be used for further risk assessment.

Table 23: DT50 values at level PI for pymetrozine in two water/sediment systems

Parent	**Distribution** (max in water 98 % after 0 days, max. in sediment 70 % after 28 d)												
Water / sediment system	**pH water phase**	**pH sed.**	**t. [°C]**	**DT_{50} [d]**	**DT_{50} [d] geo-mean**	**χ^2 [%]**	**DT_{50} [d]**	**DT_{50} [d] geo-mean**	**χ^2 [%]**	**DT_{50} [d]**	**DT_{50} [d] geomean**	**χ^2 [%]**	**Method of calcula-tion**
				total system			**water**			**sediment**			
pond Fröschweiher (pyridinyl)	8.2	6.8	20	495	395	5.4	8.5	7.9	1.9	425	346	7.3	Re-calculated SFO for system: DFOP kslow for water: FOMC DT_{90}/3.32 for sediment: SFO
pond Fröschweiher (triazinyl)	8.2	6.8	20	315		5.8	7.4		2.2	282		7.0	
Rhine, Möhlin (pyridinyl	8.4	7.1	20	289	325	3.4	9.8	11.3	2.9	265	282	4.4	
Rhine, Möhlin (triazinyl)	8.4	7.1	20	365		3.7	13.1		7.8	299		6.2	
Geometric mean (n = 2)					**358**			**9.5**			**312**		

11.4.4 Field investigations and monitoring data (if relevant for C&L)

Field investigations and monitoring data are not available.

11.4.5 Inherent and Enhanced Ready Biodegradability tests

Inherent and enhanced biodegradability test data are not available.

11.4.6 Soil and sediment degradation data

Information on ultimate biodegradability in soil and sediment is not available.

11.4.7 Hydrolysis

Experiments to investigate the hydrolysis of pymetrozine under sterile conditions showed that the active substance was stable under neutral (pH 7) and alkaline conditions (Kirkpatrick 1995a/b, McDonald 1996). Under acidic conditions, an equilibrium of pymetrozine and its hydrolysis products CGA215525 and CGA300407 was quickly reached. CGA215525 and CGA300407 were the only major metabolites in those studies, which may account up to 40 % and 60 % at pH 5, respectively. The hydrolysis half-lives for pymetrozine are about three hours at pH 1, 5-10 days at pH 5, approximately two years at pH 7. The major hydrolysis products are considered to be hydrolytically stable over a period of 30 to 35 days.

11.4.8 Photochemical degradation

The photolysis of [pyridinyl-^{14}C]- and [triazinyl-^{14}C]-pymetrozine was investigated in a study of Dixon & Gilbert (2011c) following OECD 306 in sterile, aqueous phosphate buffer at pH 7 under artificial continuous irradiation for up to 2 days using light from a Xenon lamp (> 290 nm) with light intensity of 25 W/m^2, equivalent to 1 day of UK/US summer sunlight for 24 hours continuous irradiation, with SFO DT_{50} values of < 1 days. In two previous studies, which were per-reviewed in the DAR (2004), the estimated environmental relevant half lives were 6.8 and 4.3 days for pyridinyl- and triazinyl-labelled pymetrozine at 40 °N, respectively. In the dark controls no degradation was observed.

Two transformation products were identified in the irradiated samples according to the studies of Kirckpatrick (1995a/b) and Dixon & Gilbert (2011c). The metabolite CGA300407 was isolated from the solutions treated with [pyridinyl-^{14}C]-pymetrozine with maximum amounts of 67 to 92 % AR after 2 to 32 days. CGA215525 and CGA249257 were isolated from the solutions treated with [triazinyl-^{14}C]-pymetrozine with maximum amounts of 67 to 71 % AR after 2 to 7 days and a maximum amount of 21 % AR after 38 days, respectively.

In an additional study of Mamouni (2004) the photolysis of [pyridinyl-^{14}C] pymetrozine was investigated in natural pond water at pH 8 following discontinuous irradiation (12 hours light/12 hours dark cycle) up to 29 days using light from a Xenon lamp (> 290 nm) with light intensity of 44 W/m^2. Pymetrozine degraded with a DT_{50} of 15.1 days in the irradiated system, corresponding to 22.6 ± 0.8 days natural summer sunlight at latitudes of 30°N – 50 °N. The major transformation product in this additional study was CGA300407 with a maximum amount of 71 % AR after 29 days. No degradation was observed in the dark controls.

11.5 ENVIRONMENTAL TRANSFORMATION OF METALS OR INORGANIC METAL COMPOUNDS

11.5.1 Summary of data/information on environmental transformation

Not relevant

11.6 ENVIRONMENTAL FATE AND OTHER RELEVANT INFORMATION

Other relevant information is not available.

11.7 COMPARISON WITH THE CLP CRITERIA

11.7.1 Acute aquatic hazard

For pymetrozine acute aquatic studies with fish, invertebrates and algae are available. The most sensitive endpoint is an EC_{50} = 3.06 mg/L for *Crassostrea virginica* (cf. chapter 11.1.). A substance has to be classified as **H400** (acute category 1), if the L/EC_{50} is ≤ 1 mg/l. This criterion is not fulfilled for pymetrozine.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

For pymetrozine long-term aquatic studies with fish, invertebrates and algae/aquatic plants are available. The most sensitive endpoint is a NOEC = 0.0251 mg/L for *Daphnia magna* (cf. chapter 11.2.).

According to the criteria of the 2nd ATP to the CLP Regulation, when NOEC values are available for all trophic levels, a substance is classified for aquatic chronic hazards if a NOEC or EC_{10} of ≤ 1 mg/L is obtained in a long-term aquatic toxicity study. The assignment of a hazard category depends on the NOEC value and whether the substance is rapidly degradable or not.

The log Pow of pymetrozine is -0.19 at 25°C. So there is no indication for bioaccumulation potential of pymetrozine (cf. chapter 11.3).

Pymetrozine has shown a biodegradation of 2% in 29 days in a test according to OECD guideline 301 B and has therefore to be regarded as not readily biodegradable (cf. chapter 11.4.1). The results of the biodegradation of pymetrozine in water/sediment system and abiotic degradation show that pymetrozine is considered not rapidly degradable (a degradation > 70% within 28 days) for purposes of classification and labelling (cf. chapter 11.4.3).

Therefore pymetrozine has to be classified as **H410** (chronic category 1), as the NOEC is ≤ 0.1 mg/L. The corresponding **M-factor is 1.**

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Pymetrozine should be classified as Aquatic Chronic 1 H410 – "Very toxic to aquatic organisms with long lasting effects" (M = 1) for the environment. This leads to a proposed labelling of H410 (Very toxic to aquatic life with long lasting effects), which triggers the pictogram GHS09 and the signal word "Warning" on the label. The following precautionary statements are indicated: P273, P391 and P501.

12. EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

13. ADDITIONAL LABELLING

None

14. REFERENCES

References cited for the toxicological evaluation:

Germany	2014	Final addendum to the Pymetrozine, Renewal Assessment Report, June 2014
Author 1	1996	CGA 215944 tech. (Pymetrozine): Effects on liver cell proliferation following dietary administration to female rats Report date: 1996-06-28 GLP: Y, published: N TOX9652165
Author 2	1992a	Rat oral teratogenicity - incl Amendment 1 dated 01.03.1996 + 2 dated 07.08.1997 Report date: 1992-09-22 GLP: Y, published: N ASB2012-4617
Author 2	1992b	Rabbit oral teratogenicity - incl amendment 1 dated 01.03.1996 + 2 dated 07.07.1997 Report date: 1992-09-28 GLP: Y, published: N ASB2012-4618
Author 2	1993	CGA 215944 technical: Rat dietary two-generation reproduction study Report date: 1993-11-15 GLP: yes, published: no TOX9652156
Author 3	1995a	CGA 215944 tech.: 24-month carcinogenicity and chronic toxicity study in rats Report date: 1995-10-19 GLP: yes, published: no TOX9652155
Author 3	1995b	CGA 215944 tech.: 18-month carcinogenicity study in mice Report date: 1995-10-30 GLP: yes, published: no TOX9652154
Author 4	1998	Pymetrozine: 4-week oral feeding study in rats (effect on testis) Report date: 1998-04-30 GLP: N, published: N TOX9851464 , ASB2012-4625
Author 4	1998	Pymetrozine: 4-week oral feeding study in rats (effect on seminiferous epithelial cycle in testis) Report date: 1998-05-07 GLP: N, published: N TOX9851465
Author 5	1995	CGA 215944 tech. (Pymetrozine): Effect on replicative DNA synthesis in hepatocytes following dietary administration to male mice Report date: 1995-05-16 GLP: yes, published: no TOX9650888
Author 6	2003	Pymetrozine tech. (CGA 215944): Developmental neurotoxicity study in rats Report date: 21 November 2003
Author 7	1996	Liver and thyroid medium-term bioassay for tumor promotion potential of CGA 215944 Report date: 1996-12-26 GLP: yes, published: no TOX9700527

Author 8 and Author 5	1995	CGA 215`944 tech. (Pymetrozine): Effects on selected biochemical and morphological liver parameters following dietary administration to male mice Report date: 1995-03-29 GLP: Y, published: N TOX9652160

Regarding the references cited for the environmental evaluation, please refer to the RAR (2013).