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**List of Endpoints** 

Versions of RAR, Vol 1 Quinoclamine

Date	Reason for revision
May 2018	First version submitted to EFSA
September 2018	Revised following Echa Accordance check of CLH proposal.

## Classification

Please note that the RMS has tried to use the new combined RAR/CLH template for Volume 1 (SANCO/12592/2012. rev 1.1, October 2017). This means that the structure and content of the document should serve both as a basis for decision under Regulation (EC) No 1107/2009 and as a proposal for classification under Regulation (EC) No 1272/2008.

NB: The application for renewal of Quinoclamine under EU Reg. 1107/2009 was withdrawn by the applicant shortly after submission of the RAR to EFSA in May 2018. Therefore, no EFSA peer review has taken place for the substance.

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# Level 1

## 1 Statement of subject matter and purpose for which this report has been prepared and background information on the application

## 1.1 Context in which the renewal assessment report was prepared

## 1.1.1 Purpose for which the renewal assessment report was prepared

Quinoclamine is an active substance currently approved until 31 December 2018 under Commission Regulation (EC) No. 1107/2009. This renewal assessment report (RAR) was prepared to evaluate the supplementary dossier submitted by Agro-Kanesho Co. Ltd. to support the renewal of the approval of Quinoclamine. Sweden, acting as the rapporteur member state (RMS) evaluated all aspects of the application and the supplementary dossier, in accordance with the procedures specified in Commission Implementing Regulation (EU) No. 844/2012 of 18 September 2012.

The RAR provides a discussion of relevant studies submitted for the previous EU evaluation as well as relevant new studies and information generated and submitted to support the renewal. Where necessary, studies submitted for the previous EU evaluation have been re-evaluated to allow risk assessment along current standards, and to validate previous conclusions and/or calculations.

Quinoclamine is not yet subject to harmonised classification. A proposal for harmonised classification and labelling according to the CLP criteria is included in this RAR and will also be submitted to ECHA. The structure of the RAR follows the new combined template for Assessment Reports and proposals for Harmonised Classification and Labelling (CLH reports), SANCO/12592/2012, rev. 1.1 (October 2017).

## 1.1.2 Arrangements between rapporteur Member State and co-rapporteur Member State

Germany, acting as Co-RMS, agreed to review the RAR before the submission to the Commission and EFSA.

## 1.1.3 EU Regulatory history for use in Plant Protection Products

In the EU-regulatory context, Quinoclamine was first evaluated within the programme for review of existing active substances provided for in Article 8(2) of EU Council Directive 91/414/EEC. Agro-Kanesho Co. Ltd. was the notifier and sole data submitter in support of Annex I inclusion. Sweden acted as rapporteur member state (RMS). The first draft of the previous DAR was finalised in 2005. As a result of the peer review the DAR was revised in 2007. Addenda were also produced for some of the sections of the DAR in 2007.

To support the discussions that preceded the Annex I inclusion, EFSA was given mandate to perform a peerreview and the authority delivered its conclusion on 14 November 2007 (EFSA Scientific Report (2007) 117, 1-70). The Commission then presented a Review Report (SANCO/3622/07 – rev. 1, 1 February 2008). There was no request for confirmatory data to be submitted after the inclusion in Annex I of EU Council Directive 91/414/EEC.

Quinoclamine was included in Annex I of EU Council Directive 91/414/EEC on 1<sup>st</sup> January 2009 (Commission Directive 2008/66/EC of 30 June 2008), and was subsequently approved under Regulation (EC) No. 1107/2009 (repealing Council Directive 91/414/EEC) via Commission Implementing Regulation (EU) No. 540/2011 of 25<sup>th</sup> May 2011. The current expiry date for this approval is 31 December 2018.

EFSA has published a Reasoned opinion on the review of the existing maximum residue levels (MRLs) for Quinoclamine according to Article 12 of Regulation (EC) No 396/2005 (EFSA Journal 2013;11(3):3141).

## 1.1.4 Evaluations carried out under other regulatory contexts

The RMS is not aware of any EU-evaluations of Quinoclamine carried out in the framework of other relevant EU-legislation (e.g. biocides, flavourings, food additives, cosmetics).

Quinoclamine was not included in the Inventory of Evaluations performed by the Joint Meeting on Pesticide Residues (JMPR).

No information has been provided by the applicant whether Quinoclamine has been evaluated or registered in any country outside the EU.

## **1.2** Applicant(s) information

## **1.2.1** Name and address of applicant(s) for approval of the active substance

AGRO-KANESHO CO. LTD. 7F Akasaka Shasta-East 4-2-19 Akasaka, Minato-ku Tokyo, 107-0052, Japan

European Address: Agro-Kanesho European Branch Rudolf-Kinau Weg 20 21680 Stade, Germany

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## 1.2.2 Producer or producers of the active substance

AGRO-KANESHO CO., LTD. 7F Akasaka Shasta-East 4-2-19 Akasaka, Minato-ku Tokyo, 107-0052, Japan

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Department of Registration and Regulatory Affairs

RMS: SE Co-RMS: DE

7F Akasaka Shasta-East 4-2-19
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Tokyo, 107-0052, JAPAN
E-
Tel.:
Fax

Location of the manufacturing site: See confidential Annex C in Vol. 4.

## 1.2.3 Information relating to the collective provision of dossiers

The RMS received an application for renewal of the approval of Quinoclamine only from Agro-Kanesho Co. Ltd. A collective provision of dossiers has therefore not been necessary.

## **1.3** Identity of the active substance

## 1.3.1 Common name proposed or ISO-accepted and synonyms

ISO: Quinoclamine

Synonyms: Quinoclamin, ACN, ACNQ, K-1616, Mogeton

## 1.3.2 Chemical name (IUPAC and CA nomenclature)

IUPAC: 2-amino-3-chloro-1,4-naphthoquinone CA: 2-amino-3-chloro-1,4-naphthalenedione

## 1.3.3 Producer's development code numbers

Synonym for Quinoclamine: ACN technical In toxicological reports also: Mogeton or K-1616 In phys-chem reports also: Mogeton or Mogeton techn.

## 1.3.4 CAS, EC and CIPAC numbers

CAS-No.: 2797-51-5 EEC-No.: 220-529-2 CIPAC-No.: 648

#### 1.3.5 Molecular and structural formulae, molecular mass

Molecular formula: C<sub>10</sub>H<sub>6</sub>ClNO<sub>2</sub> Molecular mass: 207.6

Structural formula:



## 1.3.6 Method of manufacture (synthesis pathway) of the active substance

For further information, please refer to the confidential Annex C in Vol. 4.

## 1.3.7 Specification of purity of the active substance in g/kg

The first Annex I-inclusion approved minimum purity of 965 g/kg, which is also proposed for the renewal. RMS agrees with the specification (see Volume 4 for further information).

## 1.3.8 Identity and content of additives (such as stabilisers) and impurities

## 1.3.8.1 Additives

For further information, please refer to the confidential Annex C in Vol. 4.

## 1.3.8.2 Significant impurities

For further information, please refer to the confidential Annex C in Vol. 4.

## 1.3.8.3 Relevant impurities

The first Annex I-inclusion approved a maximum content of 15 g/kg, which is also proposed for the renewal. RMS agrees with the specification (see Volume 4 for further information).

#### 1.3.9 Analytical profile of batches

For further information, please refer to the confidential Annex C in Vol. 4.

## **1.4** Information on the plant protection product

## 1.4.1 Applicant

The same as for the active substance, see section 1.2.1 above.

## 1.4.2 Producer of the plant protection product

Cheminova Deutschland GmbH & Co. KG Stader Elbstraße 28 21683 Stade Germany

Contact:

Agro-Kanesho European Branch Rudolf-Kinau Weg 20 21680 Stade, Germany Tel.: E-mail:

Location of the manufacturing site: See confidential Annex C in Vol. 4.

## **1.4.3** Trade name or proposed trade name and producer's development code number of the plant protection product

Trade name:	Mogeton TOP
	-

Codes:

ASU 95570 H Mogeton 50% WG Mogeton TOP 50% WG

SIT 95570H

## 1.4.4 Detailed quantitative and qualitative information on the composition of the plant protection product

## 1.4.4.1 Composition of the plant protection product

Pure active substance

content of pure active substance :	500.0 g/kg	50.0% w/w
Limits ( $\pm 25$ g/kg, as given by FAO 2010):	475 g/kg	525 g/kg

#### Technical active substance (96.5 % purity)

content of technical active substance :	518 g/kg	51.8 % w/w
Limits ( $\pm 25$ g/kg as given by FAO 2010):	493 g/kg	543 g /kg

## 1.4.4.2 Information on the active substances

Туре	Name/Code Number
ISO common name	Quinoclamine
CAS No	2797-51-5
EC No	220-529-2
CIPAC No	648
Salt, ester anion or cation present	No

#### 1.4.4.3 Information on safeners, synergists and co-formulants

For further information, please refer to the confidential Annex C in Vol. 4.

## 1.4.5 Type and code of the plant protection product

Water dispersible granules [Code: WG]

#### 1.4.6 Function

Quinoclamine is a selective herbicide and algaecide.

## 1.4.7 Field of use envisaged

The proposed representative uses of Mogeton TOP for EU authorisation are:

- Post-emergence control of a broad spectrum of common mosses and algae occurring on golf greens.
- Post-emergence control of liverwort occurring on the substrate of container-/pot-grown ornamental crops in open field or glasshouse nurseries.

#### 1.4.8 Effects on harmful organisms

Quinoclamine inhibits photosynthesis in algae, mosses and other plants by interfering the electron transfer on two target sides: ii) inhibiting the D1–protein complex of the Photosystem II (Hill-reaction) similar to other herbicides such as triazines or ureas, ii) binding at the electron-donating side of the Photosystem I. However, according to HRAC information, the detailed mechanism of action of Quinoclamine is unknown till now. For further reading on the mode of action, please refer to Volume 3 CA, section B.3.6.

The applicant reported, that according to investigations on mosses, the compound is rapidly absorbed by all green plant parts and by the rhizoids. Differing to higher plants, the translocation of the compound seems to be limited in

mosses. Warm and humid climatic conditions promote the photosynthesis inhibiting effects of the compound. Under favourable conditions mosses die off after some days. - 13 -Quinoclamine Volume 1

#### **1.5** Detailed uses of the plant protection product

#### **1.5.1** Details of representative uses

Member	Crop and/or	F	Pests	Formulatio	n		Application			Max. app	olication	rate	PHI	Remarks
state(s)	situation	G	controlled						-	per treatment		(days)		
		or		Name	Туре	a.s.	method	Timing /	No. /	kg prod.	kg a.s.	Water		
		I				conc.		season	use /	/ha	/ha	(L/ha)		
		<b>(</b> a)			(h)				crop /				(c)	
EUN(DE)	Golf greens	(a) E	Mosses	Mogeton	(D) WG	50%	Downward enraving	April		7.5	3 75	1000	(C)	Only on established greens
EU-IN (DE)	Con greens	1.	algae	TOP	wū	50%	Downward spraying	August	1	7.5	5.75	1000	11.a.	Only on established greens
EU-N	Golf greens	F	Mosses,	Mogeton	WG	50%	Hand-held Spraving	April -	1	7.5	3.75	1000	n.a.	Only on established greens. Spot application
	e		algae	TOP			(Backpack)	August						
EU-N	Golf greens	F	Mosses,	Mogeton	WG	50%	Downward spraying	April -	1	3.75	1.875	500	n.a.	Only on established greens
			algae	TOP				August						
EU-N (DE)	Nursery stock	F	Liverwort	Mogeton	WG	50%	Hand-held Spraying	April -	1	7.5	3.75	1000	n.a.	Pots on permeable sheets on the ground. No
	potted plants			TOP			(Backpack)	August						application on flowering plants
EU-N (DE)	Nursery stock	F	Liverwort	Mogeton	WG	50%	Hand-held Spraying	April -	1	3.75	1.875	500	n.a.	Pots on permeable sheets on the ground. No
	potted plants			ТОР			(Backpack)	August						application on flowering plants
EU-N (NL)	Nursery stock	F	Liverwort	Mogeton	WG	50%	Downward spraying	April -	1	2.88	1.44	800	n.a.	Pots on permeable sheets on the ground. No
	potted plants			ТОР				August						application on flowering plants
EU-N (DE)	Nursery stock	G	Liverwort	Mogeton	WG	50%	Hand-held Spraying	April -	1	7.5	3.75	1000	n.a.	Walk-in tunnel; Pots on permeable sheets on the
	potted plants			TOP			(Backpack)	August						ground. No application on flowering plants
EU-N (DE)	Nursery stock	G	Liverwort	Mogeton	WG	50%	Hand-held Spraying	April -	1	3.75	1.875	500	n.a.	Walk-in tunnel; Pots on permeable sheets on the
	potted plants			TOP			(Backpack)	August						ground. No application on flowering plants
EU (DE)	Nursery stock	G	Liverwort	Mogeton	WG	50%	Hand-held Spraying	April -	1	7.5	3.75	1000	n.a.	Greenhouse; Pots on permeable sheets on the
	potted plants			TOP			(Backpack)	August						ground
EU (DE)	Nursery stock	G	Liverwort	Mogeton	WG	50%	Hand-held Spraying	April -	1	3.75	1.875	500	n.a.	Greenhouse; Pots on permeable sheets on the
	potted plants			TOP			(Backpack)	August						ground
EU (NL)	Nursery stock	G	Liverwort	Mogeton	WG	50%	Hand-held Spraying	April -	1	1.62	0.81	450	n.a.	Greenhouse; Pots on permeable sheets on the
	potted plants			TOP			(Backpack)	August						ground

Table 1.5.1-1. GAP for the proposed representative uses of Quinoclamine (representative formulation: Mogeton TOP 50% WG).

EU-N (northern and central Europe) includes Sweden, Norway, Iceland Finland, Denmark, United Kingdom, Ireland, Belgium, The Netherlands, Luxembourg, Germany, Poland, Czech Republic, Slovakia, Austria, Hungary, Switzerland, Estonia, Latvia, Lithuania, Romania, Slovenia and northern France, according to SANCO 7525/VI/95 (23 September 2016).

a) F = field/outdoor application; G = greenhouse/tunnel application; I = indoor application

*b*) *WG* = water dispersible granules

c) PHI = minimum pre-harvest interval

#### 1.5.2 Further information on representative uses

Mogeton TOP is diluted in water and applied by tractor mounted sprayer or handheld sprayer.

During the evaluation, the RMS asked the applicant to justify why Mogeton TOP is intended for maximum one application per crop and season, considering that a treatment with Mogeton TOP protects crop only for a period of about 2-4 months. Moreover, the RMS considered that the number of applications per crop is not necessarily the same as the number of applications per season, if more than one crop per season is grown in the same place.

Regarding the use on golf greens, the applicant responded that only an unusually wet place would require more than one treatment per season against moss in lawn, since golf greens are planned to avoid standing water, i.e. the ground is practically always sloped. Based on this reasoning, the RMS accepted the restriction in the GAP table of maximum one application per season on golf greens.

Regarding the use in nursery stock potted plants, the applicant clarified that it is theoretically possible in the nurseries to have more than one treatment at a specific place. However, the treated plant pots contain multi-year ligneous plants (i.e. with wooden stems) – and are usually grown relatively large, hence keeping their position most or all of the season. Further, since even minor phytotoxic effects can make potted plants difficult to sell, and the orange colour of Quinoclamine is very intensive, Mogeton TOP is not used on, and not registered for herbaceous plants.

Mogeton TOP is not intended for use on areas where human food is cultivated, where livestock is grazing or where animal feeding stuffs are harvested. Therefore, no studies on residues in or on treated products, food or feed are necessary. Further, no re-entry period for livestock or withholding period for animal feeding stuffs need to be established. As the proposed representative uses refer to permanent crops (lawn) and special cultivation systems (containerized plants in nurseries), with maximum one application per year, recommendations concerning the influence of the product on succeeding crops are not considered relevant.

## **1.5.3** Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

Not relevant.

## 1.5.4 Overview on authorisations in EU Member States

Different formulations with Quinoclamine are widely registered in the EU for control of mosses, liverwort and algae on lawns, ways and nursery plants. Currently, solo-products with Quinoclamine for any of these purposes are authorised in Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Luxembourg,

Netherlands, Poland, Slovakia, Spain and United Kingdom. Altogether, the maximum authorised total application rate in the EU is 3.75 kg a.s./ha.

# Level 2

#### 2 Summary of active substance hazard and of product risk assessment

## 2.1 Identity

#### 2.1.1 Summary of identity

The identity of Quinoclamine is summarized in Level 1, section 1.3.

#### 2.2 Physical and chemical properties

#### 2.2.1 Summary of physical and chemical properties of the active substance

Quinoclamine is an orange solid (technical grade, 99.0 % purity). A melting point of 200-202 °C was determined for the technical grade substance (99.0 % purity). The boiling point is 348-350 °C. The vapour pressure was determined to be 7 x 10<sup>-6</sup> Pa at 25 °C and 3 x 10<sup>-6</sup> Pa at 20 °C (extrapolated values from measurements at higher temperatures). The Henry's law constant at 20°C were calculated to be 3.05 x 10<sup>-5</sup> Pa x m<sup>3</sup> x mol<sup>-1</sup>. Quinoclamine has a calculated pKa of 0.93 (deprotonation of the amino group), since no dissociation occurred between pH 2-11. The solubility in water is 20.7 mg/l  $\pm$  1.0 mg/l at pH 4 (citrate buffer), 19.8 mg/l  $\pm$  0.4 mg/l at pH 8.5 (unadjusted distilled water) and 20.7 mg/l  $\pm$  0.7 mg/l at pH 9 (borax buffer). In organic solvents the substance is soluble in acetone (12.2-12.8 g/L) but poorly soluble in the other solvents tested (1,2-dichloroethane, ethyl acetate, nheptane, methanol and p-xylene, all <10g/L). The log P<sub>ow</sub> value of the active substance was determined to be 1.58 at 30 °C and pH 11. Because of the determination at such high pH, the value was also calculated using KOWWIN. The found value of 1.50 indicated the validity of the measured value. The log Pow of the metabolites included in the residue definition for risk assessment (surface water) were predicted using KOWWIN and were all well below 3. The RMS thus considers that experimental data is not required. All spectral data is available and acceptable for the active substance itself. Since the active substance as manufactured contains a relevant impurity (dichlone), spectral data is also required for this impurity. UV-VIS, IR, NMR and MS-data is available and acceptable for dichlone.

Since the melting point is > 40 °C, flash point was not considered applicable. The active substance is not flammable, auto-flammable nor explosive and has no oxidising properties as determined in accordance with the tests recommended in the data requirements (Reg No 283/2013).

The substance should also not be classified as a flammable substance (based on negative screening test in EEC A.10 which is valid for CLP), explosive (based on structural assessment in accordance with the waiving criteria in

CLP) or oxidizing (based on structural assessment in accordance with the waiving criteria in CLP) under CLP. No other data has been provided which permits further conclusions to be made on physical hazard under CLP.

Table 2.2.1-1. Summar	v of ph	vsicochemical	properties of	f the active substance
rable mail is building	<i>y</i> or pr	y sicoenenneur	properties of	i inc active substance

Property	Value	Reference	Comment
Physical state at 20°C and 101,3 kPa	Solid	Bates, M. 2000	Visual assessment
Melting/freezing point	200-202 °C	Bates, M. 2000	Measured
Boiling point	348-350 °C	Bates, M. 2000	Measured
Relative density	1.554	Bates, M. 2000	Measured
Vapour pressure	7 x 10-6 Pa at 25 °C 3 x 10-6 Pa at 20 °C	Bates, M. 2000	Measured (extrapolated)
Surface tension	72.1 mN/m	Bates, M. 2000	Measured
Water solubility	20.7 mg/l $\pm$ 1.0 mg/l at pH 4 (citrate buffer) 19.8 mg/l $\pm$ 0.4 mg/l at pH 8.5 (unadjusted distilled water) 20.7 mg/l $\pm$ 0.7 mg/l at pH 9 (borax buffer)	Bates, M. 2000	Measured
Partition coefficient n-octanol/water	1.58 (30 °C, pH 11) 1.50 (theoretical)	Bates, M. 2000	Measured/estimated
Flash point	Not applicable		Melting point >40 °C
Flammability	Not flammable	Bates, M. 2000	Measured
Explosive properties	Not explosive	Bates, M. 2000	Calculated/measured
Self-ignition temperature	Self-ignitionThe test material did not self-ignite below 230 °C (30 °Cabove the melting point).		Measured
Oxidising properties	pperties Not oxidising		Measured
Granulometry	No data		
Solubility in organic solvents and identity of relevant degradation products	acetone: 12.2-12.8 g/l 1,2-dichloroethane: < 10 g/l ethyl acetate:< 10 g/l n-heptane:< 10 g/l methanol:< 10 g/l p-xylene < 10 g/l	Bates, M. 2000	Measured
Dissociation constant	pKa=0.93	Bates, M. 2000	Calculated since no dissociation occurs between pH 2-11.
Viscosity	Not relevant. The active substance is a solid (melting point 200-202 °C).	-	-
Active substance: Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity	UV/Vis: acidic test solutions (pH: 2.5) $\varepsilon = 14100$ at 219 nm $\varepsilon = 21500$ at 266 nm $\varepsilon = 2410$ at 339 nm $\varepsilon = 2570$ at 460 nm unadjusted test solutions (pH: 6.3) $\varepsilon = 14100$ at 219 nm $\varepsilon = 22500$ at 266 nm $\varepsilon = 2370$ at 338 nm $\varepsilon = 2550$ at 458 nm alkaline test solutions (pH: 11.0) $\varepsilon = 13900$ at 218 nm $\varepsilon = 22200$ at 267 nm $\varepsilon = 2230$ at 339 nm $\varepsilon = 22500$ at 460 nm	Bates, M. 2000	Measured

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Property	Value				Reference	Comment
	No absorbance maxima were detected above 290 nm to 700 nm.					
	IR					
	Frequency     Assignment       3411     N-H stretch       3111     Aromatic C-H stretch					
	1985-1864	Arom	atic C-H band or	vertone	Bates M	
	1686	C-C	C = O stretch		2000	Measured
	1605	Δrom	atic C-C stretch	<u> </u>	2000	
	1305-968	Arom	atic C-H in plan	e bend. C-N stretch		
	852-661	Arom	atic out of plane	bend		
	852-532	C-Cls	strech	bend		
	1H-NMR	0.011	hieen			
	Chemical Sł	$\operatorname{nift}(\delta)$	Coupling	Assignment		
	8.05		2 Doublets	H6. H9	Bates, M.	
	7.84		Triplet	H7 or H8	2000	Measured
	7.75		Triplet	H7 or H8		
	6.79		Broad singlet	NH2		
	1C NMR		8			
$ \begin{array}{c}                                     $		s Assignment C1 C4 C3 C7/C8 C5/C10	Bates, M. 2000	Measured		
	133.5		1	C7/C8		
	131.1		1	C5/C10		
	127.1		2	C6,C9		
	111.5		1	C2		
	MS (LC-MS/I	MS):				
	Peak (m/z) 208/210 180/182 182	Assign Moleco Fragm Fragm H <sub>3</sub> N <sup>+</sup>	nment cular ion: nent ion: nent ion:		Bates, M. 2000	Measured
			ö			

Property	Value		Reference	Comment
	172	Fragment ion:		
	146	Fragment ion: H <sub>2</sub> N C <sup>+</sup> O		
	105	Fragment ion:		
<u>Relevant impurity</u> (dichlone): Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity	UV-VIS, IR, acceptable and impurity.	<sup>1</sup> H- and <sup>13</sup> C-NMR and MS data are d confirms the structure of the relevant	Dardemann & Frauen 2007 (UV- VIS) Henke, 2015 (IR) Class, 2008 (NMR) Class, 2007 (MS)	Measured

## 2.2.1.1 Evaluation of physical hazards

#### 2.2.1.1.1 Explosives

Table 2.2.1.1.1-1. Summary table of studies on explosive properties

Method	Results	Remarks	Reference
Structural examination/calculation of oxygen			
balance/DSC (for enthalpies for exothermic	Not explosive		Bates, M. 2000
processes)			

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

The explosive properties of Quinoclamine were investigated by calculation of the oxygen balance and comparing bond groupings present in the molecule. The oxygen balance is 161.83 %, which is under the CLP criteria of 200 for non-explosiveness. Furthermore, Quinoclamine contains no functional groups known to confer explosive properties or explosive enhancing groups. DSC showed no exothermic processes between 20 °C and 600 °C with

enthalpies near the trigger value for explosion 500 J/g. Hence, it was considered that Quinoclamine does not present a significant risk of explosion.

## 2.2.1.1.1.2 Comparison with the CLP criteria

Quinoclamine should not be classified as explosive according to the CLP criteria of oxygen balance.

## 2.2.1.1.1.3 Conclusion on classification and labelling for explosive properties

No classification is proposed.

#### 2.2.1.1.2 Flammable gases (including chemically instable gases)

Hazard class not applicable (Quinoclamine is not a gas)

#### 2.2.1.1.3 Oxidising gases

Hazard class not applicable (Quinoclamine is not a gas)

#### 2.2.1.1.4 Gases under pressure

Hazard class not applicable (Quinoclamine is not a gas)

#### 2.2.1.1.5 Flammable liquids

Hazard class not applicable (Quinoclamine is not a liquid)

#### 2.2.1.1.6 Flammable solids

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        Table 2.2.1.1.6-1. Summary table of studies on flammable solids
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Method	Results	Remarks	Reference
EEC A.10	Material not highly flammable		Bates, 2000

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

One test performed in accordance with EEC A.10 is available. The substance did not ignite in the preliminary screening test and is thus not regarded as highly flammable in the sense of the test method.

## 2.2.1.1.6.2 Comparison with the CLP criteria

The preliminary screening test in EEC A.10 and in CLP are identical. The substance should thus not be classified as a flammable substance under CLP.

## 2.2.1.1.6.3 Conclusion on classification and labelling for flammable solids

No classification is proposed. Data is conclusive but not sufficient for classification.

## 2.2.1.1.7 Self-reactive substances

## 2.2.1.1.7.1 Short summary and overall relevance of the provided information on self-reactive substances

No data has been provided addressing this property, and this is not required. There are no chemical groups present in the molecule associated with explosive or self-reactive properties.

## 2.2.1.1.7.2 Comparison with the CLP criteria

Data lacking

## 2.2.1.1.7.3 Conclusion on classification and labelling for self-reactive substances

No classification is proposed due to lack of data.

## 2.2.1.1.8 Pyrophoric liquids

Hazard class not applicable (Quinoclamine is not a liquid)

## 2.2.1.1.9 Pyrophoric solids

## 2.2.1.1.9.1 Short summary and overall relevance of the provided information on pyrophoric solids

No specific data derived in accordance with the recommended test method in CLP have been provided. However, Quinoclamine has been handled in air within all studies available in the dossier and there are no reports of selfignition (see references in all sections).

## 2.2.1.1.9.2 Comparison with the CLP criteria

Data (experience in handling) is conclusive but not sufficient for classification.

## 2.2.1.1.9.3 Conclusion on classification and labelling for pyrophoric solids

No classification is proposed. Data (experience in handling) is conclusive but not sufficient for classification.

## 2.2.1.1.10 Self-heating substances

## 2.2.1.1.10.1 Short summary and overall relevance of the provided information on self-heating substances

Data lacking

## 2.2.1.1.10.2 Comparison with the CLP criteria

Data lacking

## 2.2.1.1.10.3 Conclusion on classification and labelling for self-heating substances

No classification is proposed due to lack of data.

## 2.2.1.1.11 Substances which in contact with water emit flammable gases

## **2.2.1.1.11.1** Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

No specific data derived in accordance with the recommended test method in CLP have been provided. However, Quinoclamine has been handled in water within many of the studies available in the dossier and there are no reports of violent reaction and emission of gas.

## 2.2.1.1.11.2 Comparison with the CLP criteria

Data (experience in handling) is conclusive but not sufficient for classification.

## **2.2.1.1.11.3** Conclusion on classification and labelling for substances which in contact with water emit flammable gases

No classification is proposed. Data (experience in handling) is conclusive but not sufficient for classification.

## 2.2.1.1.12 Oxidising liquids

Hazard class not applicable (Quinoclamine is not a liquid).

## 2.2.1.1.13 Oxidising solids

#### Table 2.2.1.1.13-1. Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
EC A.17	Not oxidizing in the sense of the test method. The	The test item:cellulose	Bates, 2000
	maximum burning rate of the reference (barium	1:9, 3:7 and 4:&	
	nitrate):cellulose mixture (3:2) was higher (1.19 mm/s)	mixtures also burned	

Method	Results	Remarks	Reference
	than the maximum burning of the test item: cellulose	to completion, but 5:5	
	mixture (2:8; 0.61 mm/s)	and 6:4 did not.	

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

One test performed in accordance with EEC A.17 is available. The test was negative in the sense of the test method.

## 2.2.1.1.13.2 Comparison with the CLP criteria

The test under EEC A.17 does not utilize the same reference standard as in the test recommended under CLP (potassium bromate). Moreover, the decision logic in CLP stipulates that the reference:cellulose mixture should also be tested in 3:7 and 2:3 ratios whereas in EEC A.17 only a 3:2 mixture could be used as in this case. Hence, the decision logic cannot be followed and it cannot be fully concluded that the test substance is not an oxidizer under CLP.

## 2.2.1.1.13.3 Conclusion on classification and labelling for oxidising solids

No classification is proposed due to lack of data.

#### 2.2.1.1.14 Organic peroxides [equivalent to section 8.14 of the CLH report template]

Hazard class not applicable (Quinoclamine is not an organic peroxide)

## 2.2.1.1.15 Corrosive to metals

## **2.2.1.1.15.1** Short summary and overall relevance of the provided information on the hazard class corrosive to metals

No data have been provided addressing this property.

## 2.2.1.1.15.2 Comparison with the CLP criteria

Data lacking

## 2.2.1.1.15.3 Conclusion on classification and labelling for corrosive to metals

No classification is proposed due to lack of data.

## 2.2.2 Summary of physical and chemical properties of the plant protection product

Mogeton Top is an orange water dispersible granule (WG). The product is not considered explosive (test method EEC A.14) or oxidizing (test method EEC A.17). It should not be classified for flammability based on flammability and auto-flammability (test methods EEC A.10, A.15). The product pH of a 1% aq. dispersion in distilled water is 6.33 at 23°C. The pour density is 0.56 g/mL and the tap density is 0.60 g/mL. All physical and chemical properties indicate that no particular problems are to be expected. No tank mixes are intended. There were no significant changes in the formulation upon storage at 54 °C in 2 weeks or during 2 years at ambient temperature. The formulation is thus considered stable to storage under the specified conditions and the commercial packaging used in the 2 years storage showed no sign of deformation or other material changes. One interim report (3 months) is available for a two years storage study of the formulation in the commercial packaging (HDPE) in which the relevant impurity dichlone is monitored using a validated analytical method. The final report needs to be evaluated when available (data gap).

## 2.3 Data on application and efficacy

## 2.3.1 Summary of effectiveness

For evaluation of the minimum effective dose rate of Mogeton TOP, the applicant referred to five efficacy studies performed in 2006 under GEP conditions. The efficacy against mosses and liverwort was tested at three application rates: 0.5 N (1875 g a.s./ha), 0.8 N (3000 g a.s./ha) and 1 N (3750 g a.s./ha). These studies are summarised in Vol. 3 CP, Annex B.3, sections B.3.9.1 and B.3.9.2.

For moss control on lawn, the following was concluded:

- At the beginning of the assessment period (1-3 WAT) the mean efficacy value achieved 87.11% for the 0.5 N rate of Mogeton TOP compared to 92.00% for the 0.8 N rate and 95.20% for the 1 N rate.
- At the time 7-8 WAT and 12-14 WAT the efficacy of the 0.5 N rate treatment had declined to lower levels but still approximately 50%.
- In conclusion, 0.5 N rate of Mogeton TOP (corresponding to 1875 g a.s./ha) also achieved good control of common mosses on lawn 1-3 WAT after one post emergence spray application.

For liverwort in containers, the following was concluded:

- At the beginning of the assessment period (1-4 WAT) the mean efficacy value achieved 74.88% for the 0.5 N rate of Mogeton TOP compared to 83.59% for the 0.8 N rate and 92.47% for the 1 N rate.
- At the time 6-10 WAT and 12-18 WAT the efficacy of the 0.5 N rate treatment had declined to lower levels but still approximately in the range 57-41%.
- In conclusion, 0.5 N rate of Mogeton TOP (corresponding to 1875 g a.s./ha) also achieved good control of liverwort in containers 1-4 WAT after one post emergence spray application.

The (even lower) rates of 1.440 kg/ha and 0.810 kg/ha listed for The Netherlands correspond to the currently registered rates in The Netherlands.

#### 2.3.2 Summary of information on the development of resistance

The applicant provided a resistance risk analysis based on the EPPO guideline PP 1/213(3), which is available in Vol. 3 CA, Annex B.3, section B.3.7.

Quinoclamine from the chemical group of quinones is not yet classified by HRAC and according to the applicant no evidence of resistance to Quinoclamine has been reported so far. Therefore, the actual resistance risk is regarded low and should be acceptable without special restrictions.

#### 2.3.3 Summary of adverse effects on treated crops

No adverse effects on treated crops are known according to the applicant.

## 2.3.4 Summary of observations on other undesirable or unintended side-effects

No undesirable or unintended side effects are known according to the applicant.

## 2.4 Further information

## 2.4.1 Summary of methods and precautions concerning handling, storage, transport or fire

#### Safe handling

Do not smoke. Keep ignition source away. Ensure good ventilation/ exhaustion at the workplace and good interior ventilation. Protect against electrostatic charges. Avoid contact with eyes and skin. Do not inhale gases/fumes/aerosols. Keep away from feedstuffs, beverages and food.

## Personal protective equipment

Wear appropriate safety glasses and face shield, as well as appropriate body protection and respiratory protection.

#### Safe storage

Keep in a dry place between 0°C and 30°C in tightly sealed containers. Ensure good ventilation/exhaustion at the workplace. Protect from heat and direct sunlight. Provide a solvent resistant, sealed floor. Store in a way that unauthorized persons and especially children do not have access.

#### Transport

#### Table 2.4.1-1. Road/ rail transport – ADR/RID

UN number:	3077
ADR Class:	9
Packaging group:	Ш
Environmental hazards:	Environmentally hazardous substance, solid, N.O.S.
UN proper shipping name:	-

UN number:	3077
OMI/IMDG Class:	9
Packaging group:	Ш
Marine Pollutant:	Yes
UN proper shipping name:	-

## Table 2.4.1-2. Marine transport - IMDG

## Fire

Use water, foam, carbon dioxide, dry chemicals, or dry sand as extinguishing media. Fire-fighters should wear positive pressure, full-face self-contained breathing apparatus. Cool fire-exposed containers. No dangerous decomposition products are anticipated in the event of a fire

## 2.4.2 Summary of procedures for destruction or decontamination

Package the waste and contact the local authorities to make sure that the waste will be led to controlled incineration or safe waste disposal according to the official regulations.

The pyrolytic behaviour of the active substance does not need to be reported as the content of halogens of the active substance in the preparation is <60%.

No other methods of safe disposal than controlled incineration are proposed.

#### 2.4.3 Summary of emergency measures in case of an accident

In case of inhalation move the victim to fresh air. Seek medical advice immediately.

In case of contact with skin take off contaminated clothing, and wash immediately affected area with plenty water and soap. Seek medical advice, if contact skin and cause irritation or anthema.

In case of contact with eyes, rinse immediately with plenty of water for several minutes; do not forget to remove lens. Seek medical advice, if in case of eye contact.

If swallowed, wash mouth with plenty water. Seek medical advice immediately. Do not induce vomiting.

In case of leakage or spill, wear respiratory protection. Avoid dust formation. Avoid breathing dust. Ensure adequate ventilation. Evacuate personnel to safe areas. Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided. Pick up and arrange disposal without creating dust. Keep in suitable, closed containers for disposal.

## 2.5 Methods of analysis

#### 2.5.1 Methods used for the generation of pre-authorisation data

## 2.5.1.1. Methods for the analysis of the active substance as manufactured

A summary of the methods applied in order to analyse the active ingredient as well as the relevant impurity Dichlone in technical grade Quinoclamine in context of five batch analyses is presented in the table below. Analytical methods for the determination of significant impurities in Quinoclamine are presented in confidential part Volume 4.

Matrix	Analyte	Type of method	Validation	References	
Technical a.s.	Quinoclamine	(HPLC/DAD (UV)),	Sufficiently validated with respect	Manella, L. (2015)	
		266 nm,	to specificity, linearity, accuracy	2771W	
		external standard method	and precision (i.e. in accordance		
			with SANCO/3030/99 rev. 4)		
Technical a.s.	Quinoclamine	(HPLC/DAD (UV)),	Sufficiently validated with respect	Marin, J. (2009)	
		266 nm,	to specificity, linearity, accuracy	1886W	
		external standard method	and precision (i.e. in accordance		
			with SANCO/3030/99 rev. 4)		
Technical a.s.	Dichlone	(HPLC/DAD (UV)),	Sufficiently validated with respect	Manella, L. (2015)	
		266 nm,	to specificity, linearity, accuracy	2771W	
		external standard method	and precision (i.e. in accordance		
			with SANCO/3030/99 rev. 4)		
Technical a.s.	Dichlone	(HPLC/DAD (UV)),	Sufficiently validated with respect	Marin, J. (2009)	
		266 nm,	to specificity, linearity, accuracy	1886W	
		external standard method	and precision (i.e. in accordance		
			with SANCO/3030/99 rev. 4)		
	Impurities <sup>a</sup>				

Table 2.5.1.1-1. Summary of analytical methods for technical active substance.

a) Details for significant impuritites are reported in Volume 4 confidential part

Table 2.5.1.1-2. Summar	y of analytical	l methods for i	formulation	analysis.
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Matrix	Analyte	Type of method	Validation	References
Mogeton Top 50 % WG	Quinoclamine	HPLC-UV	Sufficiently validated with respect to specificity, linearity, accuracy and precision (i.e. in accordance with SANCO/3030/99 rev. 4)	Dardemann, J. 2010
Mogeton Top 50 % WG	Quinoclamine	HPLC-UV	Sufficiently validated with respect to specificity, linearity, accuracy and precision (i.e. in accordance with SANCO/3030/99 rev. 4)	Dardemann, J. 2010 AB 95570-PC-032A
Mogeton Top 50 % WG	Quinoclamine	HPLC-UV	Sufficiently validated with respect to specificity, linearity, accuracy and precision (i.e. in accordance with SANCO/3030/99 rev. 4)	Thieu-Simchen V.A. 2016

Matrix	Analyte	Type of method	Validation	References
Mogeton Top 50 % WG	Dichlone	HPLC-UV	Sufficiently validated with respect to specificity, linearity, accuracy and precision (i.e. in accordance with SANCO/3030/99 rev. 4)	Thieu-Simchen V.A., 2016
ASU 95570 H	Dichlone	HPLC-UV	Sufficiently validated with respect to specificity, linearity, accuracy and precision (i.e. in accordance with SANCO/3030/99 rev. 4)	Dardemann, J., Frauen, M., 2008
	Impurities <sup>a</sup>			

a) Details are reported in Volume 4 confidential part

## 2.5.1.2. Methods for risk assessment

The methods used for generating data for risk assessment in the dossier are presented in the tables below. Most methods are considered acceptable and it can thus be confirmed that the data generated by the methods is valid. However, for some studies related to vertebrate data validation data is missing. Since it relates to vertebrate data, which should not be repeated, no data gap has been proposed.

Matrix	Analyte	Type of method Single (S) /Multi (M)	Validation	Reference
Soil	Quinoclamine	S, HPLC/UV (254 nm), TLC (254 nm)	satisfactory	Völkel W. (2015) 20140108
Soil	<sup>14</sup> C-Quinoclamine	S, HPLC/UV (254 nm), TLC (254 nm)	Not required	Adam D. (2016)
Soil	<sup>14</sup> C-Quinoclamine	LSC	Not required	Bishop, L., 2003
Soil	Phthalic acid (metabolite M6)	M, HPLC/MS (m/z 164.877 → 120.800, 77.000, 88.800)	Satisfactory	Adam D. (2016)
Soil	Phthalamic acid (metabolite M9)	M, HPLC-MS (m/z 166.062 →149.000, 121.000)	Not satisfactory (one sample per fortification level only, three fortification levels)	Piskorski R., 2016
Soil	2-Oxalyl-benzoic acid (metabolite M10)	M, LC/MS/MS	Satisfactory	Fiebig S. (2016)
Soil	2-oxamoylbenzoic acid (metabolite M11)	M, LC/MS/MS	Satisfactory	Fiebig S. (2016)
Soil	Quinoclamine	M, HPLC-MS/MS (m/z 208 $\rightarrow$ 77.1 quantification, m/z 208 $\rightarrow$ 105.1; 89.1 confirmation)	Satisfactory	Dautel P. (2016) 15 10 35 2093 Dautel P. (2016) 15 10 35 2092
Soil	Quinoclamine	GC-ECD	Satisfactory	Brielbeck, B., Marx, D., 1997 RU0896 & RU0595
Soil	<sup>14</sup> C-Quinoclamine	LSC	Not required	Lewis, C. J., 2000
CaCl <sub>2</sub> solution/soluble matrix of standard soil, soil	2-Amino-1,4- naphthoquinone (metabolite AN)	S, HPLC/UV (265 nm)	Satisfactory	Dardemann J. (2009)
Soil	Quinoclamine	GC-ECD	Not satisfactory(only accuracy data available)	Brosius, E. M., 1990

Table 2.5.1.2-1 Summary of analytical methods used for data generation for the active substance and its metabolites.

		Γ	<b>I</b>	r
Matrix	Analyte	Type of method Single (S) /Multi (M)	Validation	Reference
Water	<sup>14</sup> C-Ouinoclamine	LSC	Not required	Lewis C I 2001
Water	<sup>14</sup> C-Quinoclamine	LSC	Not required	Yeomans, P., 2003
Water	<sup>14</sup> C-Quinoclamine	LSC	Not required	Shah, J. F., 2006
Water	Quinoclamine	HPLC	Not satisfactory (only a calibration curve presented)	Werle, H., 1992
Surface water (biodegradation test)	<sup>14</sup> C-Quinoclamine	LSC	Not required	Völkel, W., 2016
Water (degradation/metabolism study)	<sup>14</sup> C-Quinoclamine	LSC	Not required	Völkel, W., 2016
Water/sediment	<sup>14</sup> C-Quinoclamine	LSC	Not required	Muttzall, P. I. 1993
Air/soil	<sup>14</sup> C-Quinoclamine	LSC/TLC	Not required	Reichert, N., 1994
Dose solution (Rat and human liver microsomes)	<sup>14</sup> C-Quinoclamine	LC-PDA-(RAD)-MS	Not required	Piñeiro Costas, N., 2016
Gravimetric filters (used in acute inhalation in rat)	Quinoclamine	Gravimeter	Not required	Van Huygevoort, A.H.B.M., 2009
Dose in air (used in inhalation 4 hours study in rats)	Quinoclamine	GC-FID	Not satisfactory (no validation data)	1986
Dose solution (used in oral 28-day study in rat)	Quinoclamine	HPLC	Not satisfactory (no raw data available)	2002, 2003
Diet feed (used in oral 13 week study in rat)	Quinoclamine	HPLC	Not satisfactory (no raw data available)	2002
Dose solution (used in 28-day dermal study in rat)	Quinoclamine	HPLC	Not satisfactory (no raw data available)	2002
Rat liver (used in unscheduled DNA synthesis/genotoxicity study)	Quinoclamine	HPLC	Not satisfactory (raw data missing for linearity and accuracy)	1996
Diet feed (used in oral 104 week study in rat)	Quinoclamine	HPLC	Not satisfactory (no raw data available)	1991
Diet feed (used in oral 80 week study in mouse)	Quinoclamine	HPLC	Not satisfactory (no raw data available)	1993
Diet feed (used in oral 4 prenatal studies in rat and rabbit (2 studies each))	Quinoclamine	HPLC	Not satisfactory (no raw data available)	2002
Dose solution (used in dermal embryo study)	Quinoclamine	HPLC	Satisfactory	1996
Grass (turf)	<sup>14</sup> C-Quinoclamine	LSC	Not required	Schnöder, F., 2003
Diet feed (used in short term toxicity study in bobwhite quail)	Quinoclamine	HPLC	Not satisfactory (raw data missing for linearity and accuracy)	2001
Diet feed (used in short term toxicity study in Mallard Duck)	Quinoclamine	HPLC	Satisfactory	, 2005
Diet feed (used in reproductive toxicity study in bobwhite quail)	Quinoclamine	HPLC	Satisfactory	., 2002
Diet feed (used in two fish toxicity studies)	Quinoclamine	HPLC	Not satisfactory (validation data missing)	1991

Matrix	Analyte	Type of method	Validation	Reference
		Single (S) /Multi (M)		
Diet feed (used in fish toxicity study)	Quinoclamine	HPLC	Satisfactory	2015
Algae Diet feed (used in fish toxicity study)	Quinoclamine	HPLC	Not satisfactory (validation data missing)	1991
Aquatic invertebrate, Daphnia magna	Quinoclamine	HPLC	Satisfactory	Jahnke, M., 1994
Larvae Chironomus riparius	Quinoclamine	HPLC	Satisfactory	Weber, H., 2000
Larvae Chironomus riparius	2-amino-1,4- naphthoquinone	HPLC	Satisfactory	Juckeland, 2009
Algae Navicula pelliculosa	Quinoclamine	HPLC	Not satisfactory (precision data is missing)	Weber, H., 2000
Aquatic plant Myriophyllum spicatum	Quinoclamine	HPLC	Satisfactory	Juckeland, D., 2015
Aquatic plant Lemna minor	Quinoclamine	HPLC	Satisfactory	Weber, H., 2000
Water various chem/phys	Quinoclamine	HPLC	Satisfactory	Bates, 2000
Grass	Quinoclamine	HPLC	Satisfactory	Dardemann, O., Frauen, M., 2005

Table 2.5.1.2-2. Summary	of analytical methods use	ed for data generation fo	or the plant protecti	on product.
Matrix	Analyta	Type of method	Validation	Reference

Matrix	Analyte	Type of method Single (S) /Multi (M)	Validation	Reference
Leaf Wash Solutions	Quinoclamine	HPLC-MS/MS	Satisfactory	Perny, A., 2016
Diet feed	Quinoclamine	HPLC	Satisfactory	Laky, V., 2008
Arthropods	Quinoclamine	HPLC-MS/MS	Satisfactory	Henkes, K., 2016
Dose solution (used in 4 fish toxicity studies)	Quinoclamine	LC-MS/MS	Satisfactory	2000
Dose solution (used in fish toxicity study)	Quinoclamine	LC-MS/MS	Satisfactory	1998
Aquatic invertebrate, Daphnia magna	Quinoclamine	HPLC	Satisfactory	Heintze, A., 1998
Algae Scenedesmus subspictus	Quinoclamine	HPLC	Satisfactory	Dangler, D., 1998
Aquatic plant Lemna minor	Quinoclamine	HPLC	Satisfactory	Juckeland, D., 2008
Dose solution (used in fish toxicity study)	Quinoclamine	LC-MS/MS	Satisfactory	2016
Aquatic invertebrate, Daphnia magna	Quinoclamine	LC-MS/MS	Satisfactory	Renner, P., 2016
Honeybee larvae Apis mellifera	Quinoclamine	HPLC	Satisfactory	Kleebaum, K., 2015
Soil mesofauna	Quinoclamine	HPLC-MS/MS	Satisfactory	Dautel, P., 2016
Spray solution (3.75 g a.i./L) Honeybee larvae Apis mellifera	Quinoclamine	HPLC	Satisfactory	Dardemann, J. 2009
Non-target plants, 2 studies	Quinoclamine	HPLC	Satisfactory	Friedrich, S., 2015

## 2.5.2 Methods for post control and monitoring purposes

New studies for post control and monitoring purposes have been evaluated in Vol. 3, section B.5.2. Suitable analytical methods for plant products are missing, which is considered as a data gap. Analytical methods for food of animal origin for monitoring purposes are not required.

An overview assessment of the submitted analytical methods for soil, water, air, body fluids and tissue showed that acceptable methods for all relevant matrices/commodity groups are available:

## Soil

For monitoring purposes a HPLC/MS/MS method was validated for analyzing Quinoclamine in soil. The daughter ions m/z 105 and m/z 172 were used for quantification and confirmation purpose, respectively. LOQ for soil was determined to be 0.05 mg/kg.

## Water

For monitoring purposes a HPLC/MS/MS method was validated for analyzing Quinoclamine in water (drinking water, surface water). The daughter ions m/z 105 and m/z 172 were used for quantification and confirmation purpose, respectively. LOQ for both drinking and surface water was determined to be  $0.1 \mu g/L$ .

## Air

As monitoring method for Quinoclamine in air we refer to a study already evaluated under 91/414/EEC, applying HPLC/MS/MS. The limit of detection was  $1.5 \ \mu g/m^3$ .

## Body fluids and tissues

For monitoring purposes HPLC/MS/MS methods were validated for analysis of Quinoclamine in both body fluids, i.e. blood and body tissues, i.e. liver and kidney. The daughter ions m/z 105 and m/z 172 were used for quantification and confirmation purpose, respectively. LOQ in blood was determined to be 0.05 mg/L. LOQ in liver and kidney was determined to be 0.01 mg/kg.

The analytical method performances were evaluated according to Guidelines SANCO/825/00 rev. 8.1. A summary of the analytical methods covering relevant residue definitions and limits is shown in Table 2.5.2-1 below.

Table 2.5.2-1. Summary of analytical methods covering relevant residue definitions and minus.						
Matrix / crop group	Analyte	LOQ	Residue limit			
Food of plant origin	Methods for foo	r food of plant origin are needed to detect misuse of Quinoclamine. The lack of				
	suitable analytical methods is therefore considered a data gap.					
Food of animal origin	Not relevant for the representative uses					
Soil	Quinoclamine	0.05 mg/kg	0.05 mg/kg (default limit)			
Surface water	Quinoclamine	0.1 µg/L	2.13 µg/L (fish NOEC)			
Drinking/ground water	Quinoclamine $0.1 \mu\text{g/L}$ $0.1 \mu\text{g/L}$ (EU drinking water limit		0.1 µg/L (EU drinking water limit)			
Air	Quinoclamine	1.5 μg/m <sup>3</sup>	$9 \mu g/m^3$ (based an AOEL of 0.03			
			mg/kg bw/day)			

 Table 2.5.2-1. Summary of analytical methods covering relevant residue definitions and limits.

Matrix / crop group	Analyte	LOQ	Residue limit
Body fluids and tissues	Quinoclamine	Body fluids (blood): 0.05 mg/L (HPLC/MS/MS)	Body fluids: 0.05 mg/L
		Body tissues (kidney, liver): 0.01 mg/kg (HPLC/MS/MS)	Body tissues: 0.1 mg/kg

## Table 2.5.2-2. Overview of accepted residue analytical methods.

Matrix / crop group	Primary method	Analyte	Confirmatory method	Independent Lab Validation (if appropriate)
Food of plant origin	Suitable methods are missing. This is considered a data gap.	-	-	-
Food of animal origin	Not required	-	-	-
Soil	KCA 4.2/01 Nichetti S. (2015) Report No. CH-562/2015 HPLC-MS/MS	Quinoclamine	No separate confirmatory method is required	-
Drinking, Ground and Surface water	KCA 4.2/02 Nichetti S. (2015) Report No. CH-561/2015 HPLC-MS/MS	Quinoclamine	No separate confirmatory method is required	KCA 4.2/03 Johannes, J. (2016) Report No. 15033001G92601
Air	KCA 4.2 c Winbush, J. Report No. 619/152-D2149 HPLC-MS/MS	Quinoclamine	No separate confirmatory method is required	-
Body fluids and tissues	Body fluids KCA 4.2/04 Seibold, A. Report No. P3911G HPLC-MS/MS Body tissues KCA 4.2/05 Seibold, A. Report No. P3912G HPLC-MS/MS	Quinoclamine	No separate confirmatory method is required	-

## 2.6 Effects on human and animal health

## 2.6.1 Summary of absorption, distribution, metabolism and excretion in mammals

			D.C.
Method, guideline, test material,	Results	Remarks	Reference
species, strain, sex			
Toxicokinetics	Oral absorption:	Acceptable	RAR Vol. 3
	Rapid (maximum concentrations in		B.6.1.1/01
OECD TG 471	blood within 1.2 and 0.25 h (single	Deviations from	
	low dose) and within 9 h and 21 h	OECD TG 471:	Anonymous
<sup>14</sup> C-Quinoclamine, purity: 99.7%	(single high dose) for males and	i Four animals (two	1(2002)
Quinoclamine, purity 00.0%	famalas raspactively	males and two	1(2002)
Valiate 0.200 a magning	Tennales, Tespectively		Danast Na
venicie: 0.3% aqueous		iemales) were used in	Keport No.:
carboxymethylcellulose	Extent: >82% (based on urinary and	the biliary	619/102-D1145
	biliary excretion plus radioactivity	investigations (the	
Rat	remaining in carcass)	guideline recommends	New data for Annex
		four animals of the	I renewal: No
Sprague Dawley Crl:CD BR	Excretion:	appropriate sex (or of	
	Rapid (greater portion of	both sexes)	
M. F	radioactivity excreted in urine and	ii. Thyroid and skin	
, -	faeces within 24 h of dose	were not collected for	
Single oral dose: 3 or 300 mg/kg	administration (single low dose)	the evaluation of tissue	
buy	Within 72 h (single high dose)	distribution	
DW	within 72 h (single high dose)	distribution	
Repeated oral dose: 3 mg/kg bw	Excretion in urine: about 62%		
for 3 or 5 days	(males) and 64% (females) (single		
	low dose) and 49% (males) and		
GLP: Yes	47% (females) (single high dose)		
	Excretion in faeces: 23% (males)		
	and 16% (famalas) (single low		
	doce) and 260( (males) and 410(		
	dose) and 50% (males) and 41%		
	(females) (single high dose)		
	Excretion in bile: about 20%		
	(males) and 25% (females) (single		
	low dose).		
	Excretion in expired air: <1% of		
	administered dose		
	administered dose		
	Distribution:		
	Widely distributed. Highest		
	radioactivity found in the carcass,		
	GI-tract, stomach, liver and the		
	kidneys. Radioactivity was rapidly		
	distributed and cleared from tissues		
	with distribution and clearence		
	with distribution and clearance		
	being slower in temales. No		
	evidence of accumulation of		
	radioactivity in any tissue following		
	either single or repeated dose		
	administration.		
	Metabolism:		
	Extensively metabolised in the rat		
	The metabolites identified were		
	mainly the product of conjugation		
	manny the product of conjugation		
	occurring on the two carbonyl		
	groups. There was also a hydrolysis		

Table 2.6.1-1. Summary table of toxicokinetic studies

Method, guideline, test material,	Results	Remarks	Reference
species, strain, sex			
	product of quinoclamine formed by		
	chlorine replacement.		
Comparative in vitro metabolism	In rat and human microsomes	No existing OECD	RAR Vol. 3
study	approximately 18% of initial	TG.	B.6.1.3/01
	Quinoclamine quantity was		
The United States Food and Drug	metabolized with half-life values	Further experiments to	Anonymous 2
Administration: Guidance for	>60 minutes. Out of sixteen	identify the chemical	(2016)
Industry: Safety Testing of Drug	detected metabolites in rat and	structure of	
Metabolites (February 2008)	human microsome incubations,	metabolites M7, M8	Report No.: 506992
	three unique metabolites (M7, M8	and M14 were not	
[1(4,5,8)- <sup>14</sup> C]Quinoclamine,	and M14) were present in the	considered necessary	New data for Annex
Radiochemical purity: 99.7%	human liver microsomal	since these metabolites	I renewal: Yes
Quinoclamine, purity: 99.9%	incubations. Based on the	were presented in liver	
	percentages of total radioactivity of	microsomes of human	
	the chromatogram, these three	at low concentrations	
Liver microsomes from male	unique human metabolites were	(<0.5% of total	
Wistar rats and male humans (pool	each <0.5% of total radioactivity.	radioactivity)	
of 25 donors)			
GLP: Yes			

M: males F: females

## 2.6.1.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

## In vivo data:

Sprague Dawley Cr1:CD BR strain rats (Charles River, UK; 150-280 g) were dosed orally with 3 and 300 mg/kg bw [<sup>14</sup>C]-Quinoclamine. The test substance was formulated in 0.3% aqueous carboxymethylcellulose. Pharmacokinetic, tissue distribution and excretion balance investigations were performed following single oral administration of nominally 3 mg/kg and 300 mg/kg body weight. A biliary excretion investigation was performed following a single administration at 3 mg/kg body weight and a tissue distribution investigation was performed following repeated oral administration at 3 mg/kg body weight. Rats were researched for blood and plasma kinetics, excretion balance, biliary excretion and tissue distribution following single and repeat oral administration is given in table below:

Dose group	Frequency of dose	Study type	Dose level		Number of	f animals
			mg/kg	MBq/kg	Males	Females
A1 pilot	Single	Excretion balance	300	4	2	2
A2 pilot	Single	Pharmacokinetic	300	4	2	2
В	Single	Excretion balance	3	4	4	4
С	Single	Excretion balance	300	4	4	4
D	Single	Pharmacokinetic	3	4	4	4
Е	Single	Pharmacokinetic	300	4	4	4
F	Single	Biliary cannulation	3	4	2	2
G	Single	Tissue distribution	3	4	16	16
Н	Single	Tissue distribution	300	4	16	16
Ι	Repeat	Tissue distribution	3	4	16	16
#### Absorption:

Absorption of radioactivity, estimated from the extent of urinary and biliary excretion plus the radioactivity remaining in the carcass, was >82%. Absorption of radioactivity was rapid (blood levels of radioactivity reached mean maximum concentrations within 1.2 h and 0.25 h in the low dose group and within 9 h and 21 h in the high dose group for males and females respectively).

#### **Distribution**:

Distribution was extensive. Radioactivity was rapidly distributed and cleared from tissues with distribution and clearance being slower in females. Repeated dose administration at the low dose level increased the rate of elimination of radioactivity. There was no evidence of accumulation of radioactivity in any tissue following either single or repeated dose administration. Highest radioactivity was found in the carcass, GI-tract, stomach, liver and the kidneys.

#### Excretion:

Elimination of radioactivity was rapid with the greater portion being recovered from urine and faeces within 24 h of dose administration at the low dose level and within 72 h at the high dose level.

Elimination via urine was about 62% (males) and 64% (females) (single oral low dose) and 49% (males) and 47% (females) (a single oral high dose). Faecal excretion was about 23% (males) and 16% (females) (single oral low dose) and 36% (males) and 41% (females) (single oral high dose). Excretion in bile was about 20% (males) and 25% (females) (a single oral low dose). In the pilot study it was determined that excretion of radioactivity in expired air was <1% of the administered dose.

# Metabolism:

Quinoclamine was extensively metabolised in the rat. Up to 15% of the urinary radioactivity, <1% of the faecal radioactivity and up to 10% of the biliary radioactivity co-chromatographed with parent compound. At least seven regions in urine, at least eight regions in faeces and at least two regions in bile co-eluted with supplied metabolite standards but the presence of these could not be confirmed by mass spectrometry. The metabolites identified were mainly the product of conjugation occurring on the two carbonyl groups. The diglucuronide, two separate N-acetyl/glucuronide/sulphate tri-conjugates, an N-acetyl/sulphate di-conjugate and a mercapturate conjugate formed by chlorine replacement were all identified. The position of glucuronide and sulphate conjugations could not be confirmed from the fragmentation patterns. There was also a hydrolysis product of quinoclamine formed by chlorine replacement. Comparison of the respective radiochromatograms showed that all the identified metabolites seemed to be present in each matrix.

The conjugated products are larger molecules and generally polar in nature. Thus, they can be readily excreted from the body, which is shown by the large amount of excreted radioactivity. The glucuronide conjugation was the most important phase II reaction leading to a decreased toxicity of the product.

# In vitro data:

In rat and human microsomes approximately 18% of initial Quinoclamine quantity was metabolized with half-life values >60 minutes. Out of sixteen detected metabolites in rat and human microsome incubations, three unique metabolites (M7, M8 and M14) were present in the human liver microsomal incubations. Based on the percentages of total radioactivity of the chromatogram, these three unique human metabolites were each <0.5% of total radioactivity. Further experiments to identify the chemical structure of metabolites M7, M8 and M14 were not considered necessary since these metabolites were presented in liver microsomes of human at low concentrations (<0.5% of total radioactivity).

Figure: Assigned structures of metabolites of [14C]-Quinoclamine following oral administration to the rat



# 2.6.2 Summary of acute toxicity

# 2.6.2.1 Acute toxicity - oral route

Table	2.6.2.1	l-1.	Summary	table of	animal	studies	on acute	oral	toxicity

Method,	Species, strain, sex,	Test substance	Dose levels,	Value	Reference
guideline,	no/group		duration of	LD50	
deviations if any			exposure		
Acute oral	Rat	Quinoclamine	200, 500, 2000	200 - 500	RAR Vol. 3
		Purity: 99.0%	mg/kg bw	mg/kg bw	B.6.2.1/01
OECD TG 423	Crl:WI(GIx/BRL/Han)BR			(M, F)	
		Vehicle: 1% methyl	Observation		Anonymous 3
GLP: Yes	M, F	cellulose	period: 15 days		(2002)
					Report No.:
There is no	3/sex/dose (200, 500 mg/kg				619/141
justification of the	bw)				
choice of vehicle					New data for
	3 females (2000 mg/kg bw)				Annex I
					renewal: No
Acute oral	Rat	Quinoclamine	300, 2000	300-2000	RAR Vol. 3
		Purity: 98.3%	mg/kg bw	mg/kg bw	B.6.2.1/02
OECD TG 420	Slc:Wistar (SPF))			(F)	
		Vehicle: 0.5%	Observation		Anonymous 4
GLP: Yes	F	carboxymethyl cellulose	period: 14 days		(2016)
		sodium (0.5 w/v%			Experiment
There is no	Sighting study:	CMC-Na)			No.: G427
justification of the	One female/dose (300, 2000				(154-768)
choice of vehicle	mg/kg bw)				
					New data for
	Main study:				Annex I
	Four females (300 mg/kg				renewal: Yes
	bw)				

M: males F: females

Table 2.6.2.1-2. Summary table of human data on acute oral toxicity

No data

Table 2.6.2.1-3. Summary table of other studies relevant for acute oral toxicity

No data

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

The acute oral  $LD_{50}$  in male and female rats was between 300 and 2000 mg/kg bw. There was no death among animals at 200 or 300 mg/kg bw. At the dose level of 2000 mg/kg bw/day all animals died.

Clinical signs noted in rats of the Crl:WI(GIxBRL/Han)BR strain at 200 mg/kg bw included discoloured urine (from 1 hr after dosing), soft and discoloured faeces (affecting the females on Day 2 only), and anogenital soiling. Recovery of surviving rats, as judged by external appearance and behaviour, was advanced by Day 3 and

completed by Day 4. At 500 mg/kg bw all rats showed discoloured urine and faeces, diarrhoea and anogenital soiling. Isolated causes of salivation, lethargy, piloerection, prone, unkempt appearance, dark faeces and a wasted appearance was seen. Clinical signs were apparent from 1 hour after dosing. Recovery of surviving rats was advanced by Day 6 and completed by Day 9. Rats treated at 2000 mg/kg bw, which all died (time of death after dosing: between 2 hrs and 2 days), showed a number of clinical signs including dyspnoea, palpebral closure, piloerection, discoloured urine (pink) and lethargy from the 1 hour observation. The majority of surviving rats dosed at 200 mg/kg bw failed to gain body weight during the firsts week of the observation period. One male rat treated at 200 mg/kg bw had gained body weight between Day -1 and Day 8. Rats treated at 500 mg/kg bw lost large amounts of body weight between Day -1 and Day 8. All surviving rats did gain body weight between Day 8 and 15 and all rats treated at 200 mg/kg bw and the female treated at 500 mg/kg bw gained overall body weight during the observation period. No macroscopic changes were observed for the majority of animals killed on Day 15. Macroscopic examination of one male treated at 500 mg/kg bw revealed enlarged kidneys. Examination of decedents treated at 500 or 2000 mg/kg bw revealed abnormal contents (orange fluid) in the stomach and small intestine of three rats. In one rat dosed at 2000 mg/kg bw abnormal contents were also found in the large intestine and caecum and the caecum was also found to be thin. The mucosal surfaces of the stomach were also orange in two individuals treated at 2000 mg/kg bw. Dark contents were apparent in the stomach and jejunum of one rat treated at 2000 mg/kg bw. The mucosal surface of the stomach of this rat was also dark. In two rats the connective tissue in the abdominal cavity was yellow. One male treated at 500 mg/kg bw had dark contents of the bladder and a female had dark areas on the lungs.

Clinical signs noted in rats of the Slc:Wistar (SPF) strain at 300 mg/kg bw included yellow-red chromaturia (from 1 to 6 hrs after dosing), loose stools (from 2 to 5 hrs after dosing), and ptosis (from 2 to 3 hrs after dosing), but these findings were slight and transient. Body weight measurement and necropsy revealed no abnormalities in any of the animals. The one animal dosed with 2000 mg/kg bw which died five hrs after administration showed clinical signs including yellow-red chromaturia, loose stools, compound-coloured faeces, irregular respiration, salivation, lethargy, ptosis, decrease in locomotor activity, soiled fur in the anogenital region and prone position.

# 2.6.2.1.2 Comparison with the CLP criteria regarding acute oral toxicity

According to the CLP Guidance, classification in Acute Tox. 4 (the lowest classification) is required for substances with oral  $LD_{50}$  of 300-2000 mg/kg bw. The  $LD_{50}$  for oral toxicity was between 300 and 2000 mg/kg bw and quinoclamine thus does fulfil the CLP classification criteria for acute oral toxicity (Acute Tox. 4). The corresponding converted oral ATE value is 500 mg/kg bw (based on Table 3.1.2 of Annex I to the CLP Regulation).

# 2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity

Classification of quinoclamine as acutely toxic by the oral route in Category 4 (H302: Harmful if swallowed) is proposed. The corresponding oral ATE value is 500 mg/kg bw.

#### 2.6.2.2 Acute toxicity - dermal route

Table 2.6.2.2-1. Summary table of animal studies on acute dermal toxicity

Method, guideline,	Species, strain, sex,	Test	Dose levels,	Value	Reference
deviations if any	no/group	substance	duration of	LD50	
			exposure		
Acute dermal	Rat	Quinoclamine	2000 mg/kg bw	>2000	RAR Vol. 3
		Purity: 99.0%		mg/kg bw	B.6.2.2/01
OECD TG 402	Crl:WI(GIx/BRL/Han)BR	-	Observation	(M, F)	
	, , , , , , , , , , , , , , , , , , ,		period: 15 days		Anonymous 5
GLP: Yes	M. F		r		(2002)
					()
	Preliminary study:				Report No ·
	2 females (2000 mg/kg by)				610/1/3-D61//
	Main study				01)/145-D0144
	$\frac{1}{5}$				N 1.4.6
	5/sex (2000 mg/kg bw)				New data for
					Annex I renewal:
					No

#### Table 2.6.2.2-2. Summary table of human data on acute dermal toxicity

No data

#### Table 2.6.2.2-3. Summary table of other studies relevant for acute dermal toxicity

No data

#### 2.6.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

The acute dermal LD<sub>50</sub> in male and female rats exceeded 2000 mg/kg bw. No adverse clinical signs were observed. Principal signs of reaction to treatment were staining of the snout noted from 30 minutes or 1 hour after dosing and orange coloured urine apparent from Days 2 and 4. Recovery of rats as judged by external appearance and behaviour, was complete by Day 5. Slight erythema affecting two females between Days 4 and 9 and orange staining throughout the observation period. During the first week of the observation period the majority of animals lost body weight, failed to gain body weight or achieved only modest body weight gains. All rats gained weight between Day 8 and day 15. However, one male failed to regain its pre-study body weight and the body weight gain in some individuals was only modest. No macroscopic changes were observed in animals killed on Day 15.

#### 2.6.2.2.2 Comparison with the CLP criteria regarding acute dermal toxicity

According to the CLP Guidance, classification in Acute Tox. 4 (the lowest classification) is required for substances with dermal  $LD_{50}$  of 1000-2000 mg/kg bw. The  $LD_{50}$  for dermal toxicity was above 2000 mg/kg bw, and quinoclamine thus does not fulfil the CLP classification criteria for acute dermal toxicity.

#### 2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

No classification is proposed for quinoclamine.

#### 2.6.2.3 Acute toxicity - inhalation route [equivalent to section 10.3 of the CLH report template]

Method,	Species,	Test substance, form	Dose levels,	Value	Reference
guideline,	strain, sex,	and particle size	duration of	LC50	
deviations if any	no/group	(MMAD)	exposure		
Acute inhalation	Rat	ACN technical	0.79 mg/L (4 hrs,	LC <sub>50</sub> (4 hrs, respirable	RAR Vol. 3
		(Quinoclamine)	whole body) (highest	fraction): >0.32 mg/L	B.6.2.3/01
Guideline: not	Wistar	Purity: 98.1%	attainable	(value corrected for the	
stated in the			concentration)	respirable fraction of	Anonymous 6
study report	M, F	Aerosol		the generated dust,	(1986)
			Observation period:	40%)	
GLP: Yes	5/sex	About 40% by weight of	14 days		Report No.:
		the test substance in the			TXC 3/86432
The study is not		chamber air was 5.5 µm			
acceptable due to		or less			New data for
low amount of					the Annex I
respirable					renewal: No
particles					

Table 2.6.2.3-1. Summary table of animal studies on acute inhalation toxicity
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#### Table 2.6.2.3-2. Summary table of human data on acute inhalation toxicity

No data

#### Table 2.6.2.3-3. Summary table of other studies relevant for acute inhalation toxicity

No data

#### 2.6.2.3.1. Short summary and overall relevance of the provided information on acute inhalation toxicity

An acute inhalation toxicity study in the rat is available (study previous evaluated in DAR 2005). The acute inhalation  $LC_{50}$  for male and female rats in the study was >0.32 mg/L. No deaths were observed. Abnormal body posture, abnormal respiratory pattern and rubbing of the snout or paws against the mesh of the exposure compartment were observed in a proportion of rats exposed to quinoclamine. These signs were considered to be consistent with the response to exposure to an irritant dust. A lesion involving the cornea (keratitis) and resulting in some opacity in the eye was evident, in a proportion of rats exposed to the test substance, from Day 2 of the observation period. This sign persisted, particularly in females, during the entire observation period. There was also a marked decrease of bodyweight over a period of 5 days following exposure to quinoclamine. Subsequently the rate of bodyweight gain was similar to or in excess of that observed for the control rats. Furthermore, there was a marked to moderate reduction in food consumption for 6 days in male rats and for 7 days in female rats following exposure to quinoclamine, and water consumption was reduced for 2-7 days following exposure. Following changes were observed during the necropsy: penis was inflamed and of swollen appearance in 2 male rats exposed to quinoclamine, and the fur and tail of all exposed rats were stained orange.

The study was conducted according to GLP but the study is considered of limited usefulness due to low amount of respirable particles (about 40% by weight of the test substance in the chamber air was 5.5 µm or less).

Furthermore, the concentration used in the study was low (0.79 mg/L, highest attainable concentration). According to the CLP Guidance (3.1.2.3.2) inhaled particles between 1 and 4 microns mean mass aerodynamic diameter (MMAD) will deposit in all regions of the rat respiratory tract. This particle size range corresponds to a maximum dose of about 2 mg/L. In order to achieve applicability of animal experiments to human exposure, dusts and mists would ideally be tested in this range in rats.

As a conclusion the study was considered not acceptable due to low amount of respirable particles, also taking into consideration that the mode of exposure was whole-body and not nose-only which is recommended in the OECD TG 403.

# 2.6.2.3.2. Comparison with the CLP criteria regarding acute inhalation toxicity

According to the CLP Guidance (Table 3.1.1) substances can be allocated to one of four toxicity categories based on acute toxicity by the inhalation route as shown in table below:

	Category 1	Category2	Category 3	Category 4
Dusts and Mists (mg/l)	$ATE \le 0.05$	$0.05 < ATE \le 0.5$	$0.5 < ATE \le 1.0$	$1.0 < ATE \le 5.0$
(4 hr testing exposure)				

The LC<sub>50</sub> for inhalation toxicity was greater than 0.32 mg/L for both sexes. However, the study was not acceptable due to low amount of respirable particles. Of particular importance in classifying for inhalation toxicity is the use of well articulated values in the highest hazard categories for dusts and mists. Inhaled particles between 1 and 4 microns mean mass aerodynamic diameter (MMAD) will deposit in all regions of the rat respiratory tract. This particle size range corresponds to a maximum dose of about 2 mg/l. In order to achieve applicability of animal experiments to human exposure, dusts and mists would ideally be tested in this range in rats (Annex I: 3.1.2.3.2 to the CLP Regulation). Results from studies in which substances with particle size with a MMAD > 4  $\mu$ m have been tested can generally not be used for classification, but expert judgement is needed in cases where there are indications of high toxicity.

# 2.6.2.3.3. Conclusion on classification and labelling for acute inhalation toxicity

No conclusion on classification and labelling for acute inhalation toxicity could be drawn. A **data gap** is identified for this endpoint.

# 2.6.2.4 Skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results - Observations and time point of onset2 - Mean scores/animal - Reversibility	Reference
Dermal	Rabbit	ACN technical	0.5 g/animal	One hour after removal of the patches and	RAR Vol. 3
irritation		(Quinoclamine)	-	excess test material, the treated sites of	B.6.2.4/01
			Examination	one of 6 rabbits showed a very slight	
		Purity: 98.1%	after 1, 24, 48,	erythema (score 1), but the effect was not	

Table 2.6.2.4-1. Summary table of animal studies on skin corrosion/irritation

Guideline:	New	72 and 168	reported thereafter at 24-169 hours after	Anonymous 7
Not stated in	Zealand	hours	patch removal. No other signs of	(1985)
study report	White		erythema or oedema were observed in	Report No.:
			any of the test animals.	105/8509
GLP: Yes	6 females			
				New data for
				the Annex I
				renewal: No

#### Table 2.6.2.4-2. Summary table of human data on skin corrosion/irritation

No data

Table 2.6.2.4-3. Summary table of other studies relevant for skin corrosion/irritation

No data

#### 2.6.2.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

In a study performed in accordance with GLP, 6 female New Zealand White rabbits each received dermal treatments with 0.5 g of quinoclamine for 4 hours under occlusive conditions. After four hours the dressing was removed and the treated areas gently cleaned using cotton wool soaked in water at 37°C. One hour after removal of the patches and excess test material, the treated sites were assessed for signs of reaction to treatment. Similar examinations were undertaken twenty four, forty eight, seventy two and one hundred sixty eight hours after patch removal. No dermal irritation was observed in 5 rabbits during the study. One rabbit exhibited slight erythema (score 1) one hour after removal of the patches and excess test material, but no dermal irritation was observed throughout the remainder of the study. Orange staining of skin was noted in all animals at the 1 hr observation but not at the 24, 48, 72 or 168 hr observations.

The RMS considers the study as acceptable. It was checked for compliance with OECD TG 404 and following deviations were noted:

i. No initial testing was performed using one animal

ii. Six animals were used in the study (the guideline recommends two or three animals to be used in the case a corrosive effect is not observed)

iii. The humidity of the experimental animal room was in the range of 63-81% (the guideline recommends that the relative humidity of the experimental animal room does not exceed 70%)

iv. No raw data was available.

#### 2.6.2.4.2 Comparison with the CLP criteria regarding skin corrosion/irritation

According to the CLP Guidance Table 3.2.2, a substance should be classified in Category 2 (Irritant) if:

"-mean value of  $\geq 2.3 - \leq 4.0$  for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or

-inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above"

In the skin irritation test conducted with quinoclamine no oedema/eschar was noted, and the mean value for erythema was below 2.3. Furthermore, no inflammation persisted to the end of the observation period. Thus, quinoclamine does not fulfil the CLP classification criteria as irritating to skin.

# 2.6.2.4.3 Conclusion on classification and labelling for skin corrosion/irritation

No classification is proposed for quinoclamine.

# 2.6.2.5 Serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results - Observations and time point of onset - Group mean scores (24, 48 and 72 hours) - Reversibility	Reference
Eye irritation	Rabbit	ACN technical (Quinoclamine)	0.1 mL aliquot (weighing 0.06	Scores (unrinsed group / rinsed group):	RAR Vol. 3 B.6.2.5/01
Guideline: Not stated in study	New Zealand White	Purity: 98.1%	g)/animal	Conjunctivae:	Anonymous 8
report		1 41109: 2011/0	Examination after 1,	$\frac{\text{Conjunctive:}}{\text{Chemosis: } 2.1 / 0.0}$	(1985)
GLP: Yes	6 females (not rinsed after dosing)		24, 48, 72, 168 and 336 hours	Discharge: <b>0.6</b> / 0.0 Redness: <b>1.8</b> / 0.6	Report No.: 106/8509
	3 females (rinsed with distilled water 2 min. after dosing)			<u>Cornea:</u> Opacity: <b>0.9</b> / 0.1 Iris:	New data for the Annex I renewal: <b>No</b>
				Iritis: <b>0.7</b> / 0.0 No reaction to treatment remained 14 days after dosing.	

#### Table 2.6.2.5-1. Summary table of animal studies on serious eye damage/eye irritation

 Table 2.6.2.5-2. Summary table of human data on serious eye damage/eye irritation

No data

#### Table 2.6.2.5-3. Summary table of other studies relevant for serious eye damage/eye irritation

No data

# 2.6.2.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

In a study performed in accordance with GLP, 0.1 ml of quinoclamine was placed in the lower conjunctival sac of the right eye of 9 female rabbits. The treated eyes of the first group of six rabbits (6 animals) were not rinsed after dosing with the test substance. The treated eyes of the three rabbits in second group were rinsed approximately two minutes after dosing. Each eye was rinsed over a one minute period using distilled water at 37°C. Reaction to treatment was assessed 1, 24, 48, 72, 168 and 336 hours after dosing. The eyes were assessed for damage or irritation to the cornea, iris and conjunctivae using the untreated eye as a control.

The RMS considers the study as acceptable. It was checked for compliance with OECD TG 405 and following deviation was noted:

i. The humidity in the experimental room was in the range of 57-81% (the guideline recommends the relative humidity not to exceed 70%)

ii. Group of animals was used to investigate the influence of washing (this is not recommended in the guideline unless it is scientifically justified, and if a satellite group is needed, two rabbis should be used).

One hour after dosing well defined redness and severe chemosis of the conjunctivae were apparent in all six rabbits of the unrinsed group, four of these rabbits also exhibiting iris inflammation in the treated eye. Some changes in response had occurred within twenty four hours of dosing, severe conjunctival irritation maintained by two rabbits, moderate conjunctival exhibited by two rabbits and well defend conjunctival irritation present in the treated eye of the remaining two rabbits of this group. Corneal opacity was observed in the treated eye of four rabbits and iris inflammation was also apparent in four rabbits at this time. Marked reduction in irritation had occurred in two animals of the group at the forty eight hour observation but iris inflammation, corneal opacity and moderate or severe conjunctival irritation showed some decline seventy two hours after dosing and at the one hundred and sixty eight hour observation small areas of corneal opacity remained in the treated eye of two rabbits, other irritant reaction having declined. No reaction to treatment remained fourteen days after dosing.

Severe conjunctival irritation was observed in the treated eye of two rabbits of the rinsed group one hour after dosing, the remaining rabbit of the group exhibiting a well defined conjunctival response. Twenty four hours after dosing a small area of corneal opacity and slight conjunctival redness was observed in one animal and well defined conjunctival redness was observed in the treated eye of a second rabbit of the group. This reaction declined, slight conjunctival redness remaining in both animals at the forty eight hour observation. No further response to treatment was apparent.

The results indicated that the test substance had a moderate irritant effect in the eye, with the effect being reversible. Rinsing the material from the eye within two minutes of its administration markedly reduced the severity, incidence and duration of the irritant response observed.

# 2.6.2.5.2 Comparison with the CLP criteria regarding serious eye damage/eye irritation

According to the CLP Guidance Table 3.3.2, a substance should be classified in Category 2 (Irritating to eyes) " If it produces, at least in 2/3 animals, a positive response of: -corneal opacity  $\geq 1$  and/or -iritis  $\geq 1$ , and/or -conjunctival rednesss  $\geq 2$  and/or -conjunctival oedema (chemosis)  $\geq 2$ calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days"

In the eye irritation test conducted with quinoclamine, mean scores for chemosis was > 2 in the unrinsed group Thus, quinoclamine does fulfil the CLP classification criteria for eye irritation.

# 2.6.2.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Classification of quinoclamine for eye irritation in Category 2 (H319: Causes serious eye irritation) is proposed.

# 2.6.2.6 Respiratory sensitisation

Table 2.6.2.6-1. Summary table of animal studies on respiratory sensitisation

No data

Table 2.6.2.6-2. Summary table of human data on respiratory sensitisation

No data

Table 2.6.2.6-3. Summary table of other studies relevant for respiratory sensitisation

No data

# 2.6.2.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No data

# 2.6.2.6.2 Comparison with the CLP criteria regarding respiratory sensitisation

Not relevant as no data are available

# 2.6.2.6.3 Conclusion on classification and labelling for respiratory sensitisation

Not relevant as no data are available

#### 2.6.2.7 Skin sensitisation

Table 2.6.2.7-1. Summar	y table of animal studie	es on skin sensitisation
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Method,	Species,	Test	Dose levels	Results	Reference
guideline,	strain, sex,	substance	duration of		
deviations if	no/group		exposure		
any					
Guinea Pig	Guinea pig	Quinoclamine	1st screening study:	Quinoclamine elicited a positive	RAR Vol. 3
Maximisation			0.25 - 10%  w/v	response, indicative of skin	B.6.2.6/01
Test (GPMT)	Dunkin-	Purity: 99.0%		sensitisation (delayed contact	
	Hartley		2nd screening study:	hypersensitivity) in eight of the ten	Anonymous
OECD TG 406		Vehicle:	10 – 55% w/w	test animals following the challenge	9 (2001)
	F	arachis oil		application (80%). An inconclusive	
GLP: Yes			3rd screening study:	response was seen in one further	Report No.:
	2 females		20 – 55% w/w	animal and negative results in the	619/119-
There is no	(1 <sup>st</sup>			remaining test animal.	D6144
justification of	screening		<u>Main study:</u>		
the choice of	study)		Intradermal		New data
vehicle			injection: 1% m/v		for Annex I
	2 females		Quinoclamine in		renewal: No
	(2 <sup>nd</sup>		arachis oil and/or		
	screening		Freund's complete		
	study)		adjuvant (FCA).		
	3 females		Topical induction:		
	(3 <sup>rd</sup>		55% m/m		
	screening		Quinoclamine in		
	study)		arachis oil.		
	Main study:		Challenge		
	5 females in		application: 7.5 and		
	control		15% m/m		
	group and 10		Quinoclamine in		
	females in		arachis oil		
	test group				

#### Table 2.6.2.7-2. Summary table of human data on skin sensitisation

No data

#### Table 2.6.2.7-3. Summary table of other studies relevant for skin sensitisation

No data

#### 2.6.2.7.1 Short summary and overall relevance of the provided information on skin sensitisation

The skin sensitisation potential of quinoclamine was assessed in one study (GPMT). The intradermal injection was 1% m/v quinoclamine in arachis oil and/or adjuvant, the topical induction was 55% m/m quinoclamine in arachis oil and the challenge application was 7.5 and 15% m/m in arachis oil. Quinoclamine elicited a positive response, indicative of skin sensitisation (delayed contact hypersensitivity) in eight of the ten test animals following the

challenge application (80%). An inconclusive response was seen in one further animal and negative results in the remaining test animal.

# 2.6.2.7.2 Comparison with the CLP criteria regarding skin sensitisation

According to CLP Regulation 3.4.2.2.4, a response of at least 30% of the animals is considered as positive when an adjuvant type guinea pig test method for skin sensitisation is used. Quinoclamine caused a positive response in 80% of the animals in a GPMT test with intradermal induction of 1%. Thus, quinoclamine fulfils the CLP classification criteria as a skin sensitiser.

The CLP Regulation allows classification of skin sensitisers in one hazard category, Category 1, which comprises two sub-categories, 1A and 1B. Classification into sub-categories is only allowed if data are sufficient (CLP Annex I, 3.4.2.2.1.1). Therefore care should be taken when classifying substances into Category 1B when Category 1A cannot be excluded. In such cases classification into category 1 should be considered. This is particularly important if only data are available from certain tests showing a high response after exposure to a high concentration but where lower concentrations which could show the presence of such effects at lower doses are absent (in line with some test protocols where a maximised dose should be used). The criteria for sub-categorisation based on results from Guinea pig maximisation tests are given in table below:

Sub-category	Assay	Response
1A	Guinea Pig Maximisation Test	≥30% responding at ≤0.1% intradermal
		induction dose or ≥60% responding at
		>0.1% to $\leq$ 1% intradermal induction
		dose
1B	Guinea Pig Maximisation Test	$\geq$ 30% to <60% responding at >0.1% to
		$\leq 1\%$ intradermal induction dose or
		≥30% responding at >1% intradermal
		induction dose

According to table above, quinoclamine fulfils the criteria for sub-categorisation in category 1A (Guinea Pig Maximisation Test: >60% responding at 1% intradermal induction dose).

# 2.6.2.7.3 Conclusion on classification and labelling for skin sensitisation

Classification of quinoclamine as a skin sensitiser (Skin Sens. 1A, H317: May cause an allergic skin reaction) is proposed.

# 2.6.2.8 Phototoxicity

 Table 2.6.2.8-1. Summary table of studies on phototoxicity

Method,	Test substance	Dose levels	Results	Reference
guideline,		duration of		
deviations if any		exposure		

RMS: SE
Co-RMS: DE

In vitro 3T3	Quinoclamine	31.6, 10.0, 3.16,	-UV OD540, -UV SEM:	RAR Vol. 3
NRU	-	1.00, 0.316,	IC <sub>50</sub> : 3.59 µg/mL	B.6.2.7/01
phototoxicity test	Purity: 98.3%	0.100, 0.0316		
1 5	5	and 0.0100	+UV OD <sub>540</sub> , -UV SEM:	Anonymous 10
Balb/c 3T3		ug/mL	IC <sub>50</sub> : 3.23 ug/mL	(2015)
fibroblast cells		10	10	( /
(clone 31, mouse		Final	PIF: 1.11	Report No.:
fibroblast cell		concentration of		508771
line)		DMSO in culture	Ouinoclamine is non-phototoxic (PIF	000111
		medium:	factor of $<2$ )	Anonymous 10
OECD TG 432		1000000000000000000000000000000000000		(2015)
0100 10 102		1.070 (171)		(Report
GLP· Yes		Incubated with		amendment
GEI : 103		Neutral Red for		number 1)
		approximately		number 1)
		3.5 h		New data for
		5.5 11		Anney I renewal
				Voc
				1 (5

OD: optical density

IC<sub>50</sub>: cell viability reduced to 50% PIF: Photo Irritation Factor

#### Table 2.6.2.8-2. Summary table of human data on phototoxicity

No data

# Table 2.6.2.8-3. Summary table of other studies relevant for phototoxicity

No data

# 2.6.2.8.1 Short summary and overall relevance of the provided information on phototoxicity

Quinoclamine technical was evaluated for phototoxicity in the *in vitro* 3T3 NRU at concentrations of 31.6, 10.0, 3.16, 1.00, 0.316, 0.100, 0.0316 and 0.0100  $\mu$ g/mL. Since quinoclamine had a PIF factor below 2, quinoclamine is non-phototoxic.

# 2.6.2.9 Aspiration hazard

# Table 2.6.2.9-1. Summary table of evidence for aspiration hazard

No data

# 2.6.2.9.1 Short summary and overall relevance of the provided information on aspiration hazard

No data

# 2.6.2.9.2 Comparison with the CLP criteria regarding aspiration hazard

Not relevant as no data are available

# 2.6.2.9.3 Conclusion on classification and labelling for aspiration hazard

Not relevant as no data are available

# 2.6.2.10 Specific target organ toxicity-single exposure (STOT SE)

Table 2.6.2.10-1. Summary table of animal studies on STOT SE (specific target organ toxicity-single exposure)

	r	r	r
Method, guideline,	Test substance,	Results	Reference
deviations if any,	route of	- NOAEL/LOAEL	
species, strain, sex,	exposure, dose	- target tissue/organ	
no/group	levels, duration	- critical effects at the LOAEL	
	of exposure		
Acute oral	Quinoclamine	LD <sub>50</sub> : 200 - 500 mg/kg bw (M, F)	RAR Vol. 3
	Purity: 99.0%		B.6.2.1/01
OECD TG 423	Vehicle: 1%	<u>200 mg/kg bw:</u>	
	methyl cellulose	There were no deaths. Discoloured urine from 1 hr	Anonymous 11 (2002)
There is no justification		after dosing, affecting all animals. Soft and	Report No.: 619/141
for the choice of vehicle	200, 500, 2000	discoloured faeces affecting the females on Day 2.	
	mg/kg bw	Anogenital soiling in one female from 4 hrs after	New data for Annex I
Rat		dosing and complete by Day 4	renewal: No
Crl:WI(GIx/BRL/Han)BR	Observations in		
	15 days	<u>500 mg/kg bw:</u>	
M, F		1 male and two females died. All rats showed	
2/ /1 /200 500		discoloured urine and faeces, diarrhoea and	
3/sex/dose (200, 500		anogenital soiling. Isolated causes of salivation,	
mg/kg bw)		lethargy, piloerection, prone, unkempt	
		appearance, dark faeces and a wasted appearance	
3 females (2000 mg/kg		were seen. Clinical signs were apparent from 1	
bw)		hour after dosing. Recovery of surviving rats was	
CLD V		advanced by Day 6 and complete by Day 9.	
GLP: Yes		Macroscopic examination of one male revealed	
		contants of the bladder and a famale had dark	
		contents of the bladder and a female had dark	
		areas on the lungs.	
		2000 mg/kg byy/day:	
		<u>2000 llig/kg bw/day.</u>	
		signs including dysphoes, palaebral closure	
		signs including dysphoea, parpeoral closure,	
		from the 1 hour observation A rat had straub tail	
		and was prone and another showed spacificity prior	
		to death A further rat appeared to have recovered	
		from signs of toxicity by Day 2 but by Day 3 it	
		showed palpebral closure, a wasted appearance	
		discoloured faeces (dark) and anogenital soiling	
		on Day 3 and 4. Macroscopic examination of	
		decedents revealed enlarged kidneys, abnormal	
		contents (orange fluid) in the stomach and small	
		intestine of three rats. In one rat abnormal	
		contents were also found in the large intestine and	
		caecum, and the caecum was also found to be thin.	
		The mucosal surfaces of the stomach were also	
		orange in two individuals. Dark contents were	
		apparent in the stomach and jejunum of one rat.	
		The mucosal surface of the stomach of this rat was	
		also dark. In two rats the connective tissue in the	
		abdominal cavity was yellow.	

	-		-
Acute oral	Quinoclamine	300-2000 mg/kg bw (F)	RAR Vol. 3
	Purity: 98.3%		B.6.2.1/02
OFCD TG 420		300 mg/kg hw:	
0200 10 420	Vehicle: 0.5%	There were no deaths Animals administered 300	Anonymous $1$ (2016)
	venicie. 0.570	malka showed vellow red shremeturis (from 1 to	Experiment No. (2010)
D. (	carboxymethyl	ing/kg showed yenow-red chromaturia (from 1 to	Experiment No.: $6427$
Rat	cellulose sodium	6 hrs after dosing), loose stools (from 2 to 5 hrs	(154-768)
	(0.5 w/v%	after dosing), and ptosis (from 2 to 3 hrs after	
Slc:Wistar (SPF))	CMC-Na)	dosing), but these findings were slight and	New data for Annex I
		transient. Body weight measurement and necropsy	renewal: Yes
F	300, 2000	revealed no abnormalities in any of the animals.	
	mg/kg hw		
Sighting study	88	2000 mg/kg hw	
One female/dose $(300)$	Observation	1 animal dosed died five hours after	
2000  mg/kg hw	poriod: 14 days	administration and the clinical signs observed	
2000 mg/kg 0w)	period. 14 days		
		started one nour alter administration of the test	
Main study:		substance. The observations included; yellow-red	
Four females (300 mg/kg		chromaturia, loose stools, compound-coloured	
bw)		faeces, irregular respiration, salivation, lethargy,	
		ptosis, decrease in locomotor activity, soiled fur in	
GLP: Yes		the anogenital region, prone position. The animal	
		showed loss of locomotor activity and lateral	
There is no justification		position at 4 hrs after dosing and died at 5 hrs	
for the choice of vehicle		after the dosing. No abnormal changes were	
5 5		observed in any organs at necropsy.	
Acute dermal	Quinoclamine	>2000  mg/kg bw (M, F)	RAR Vol. 3
	Purity: 99.0%		B 6 2 2/01
OECD TG 402	1 unty. 99.070	There were no deaths, and clinical signs were	<b>D</b> .0.2.2/01
OECD 10 402	2000 mg/kg hu	limited to appagnitel solling from 4 hours often	$A_{nonumous}$ 12 (2002)
B (	2000 mg/kg bw	innited to anogenital solling from 4 hours after	Anonymous 15 (2002)
Kat		dosing and pink coloured urine on the liner under	
	Observation	the cage on Days 3 and 4. Anogenital soiling was	Report No.: 619/143-
Crl:WI(GIx/BRL/Han)BR	period: 15 days	no longer apparent on Day 3 and is associated	D6144
		with the bandaging procedure and not to toxic	
M, F		effects of the test article. Discolouration of the	New data for Annex I
		urine could be attributed to elimination of	renewal: No
Preliminary study:		absorbed test article. The dermal test sites were	
2 females (2000 mg/kg		stained orange throughout the observation period.	
bw)		Necropsy on Day 8 revealed no microscopic	
Main study:		changes.	
5/sex (2000 mg/kg bw)		Besi	
5/3CA (2000 mg/Kg 0W)			
CLD: Ves			
GLP: Yes			

	<del></del>	T	<b>T</b>
Acute inhalation	ACN technical	LC <sub>50</sub> (4 hrs, respirable fraction): >0.32 mg/L	RAR Vol. 3
	(Quinoclamine)	(value corrected for the respirable fraction of the	B.6.2.3/01
Guideline: not stated in	Purity: 98.1%	generated dust, 40%)	
the study report			Anonymous 14 (1986)
	Form and	There were no deaths	-
Rat	particle size		Report No.: TXC
	(MMAD):	Clinical signs during the exposure:	3/86432
Wistar	Aerosol. About	Abnormal body posture, abnormal respiratory	
	40% by weight	pattern and rubbing of the snout or paws against	New data for the Annex I
M, F	of the test	the mesh of the exposure compartment were	renewal: No
	substance in the	observed in a proportion of rats exposed to ACN	
5/sex	chamber air was	(technical). These signs were considered to be	
	5.5 µm or less	consistent with the response to exposure to an	
GLP: Yes		irritant dust.	
	Dose level:		
The study is limited due to	0.79 mg/L (4	Clinical signs during the observation period:	
low amount of respirable	hrs, whole	A lesion involving the cornea (keratitis) and	
particles (study not	body) (highest	resulting in some opacity in the eye was evident,	
accepted for the purpose	attainable	in a proportion of rats exposed to ACN	
of classification for acute	concentration)	(technical), from Day 2 of the observation period.	
toxicity)		This sign persisted, particularly in females, during	
	Observation	the entire observation period. Inflammation of the	
	period: 14 days	penis was seen in a proportion of the male	
		exposed rats from Day 5 to Day 14 of the	
		observation period.	

 Table 2.6.2.10-2. Summary table of human data on STOT SE (specific target organ toxicity-single exposure)

Type of	Test	Route of exposure	Observations	Reference
data/report	substance	Relevant information about the		
-		study (as applicable)		
No data				

 Table 2.6.2.10-3. Summary table of other studies relevant for STOT SE (specific target organ toxicity-single exposure)

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data				

# **2.6.2.10.1** Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure (STOT SE)

Following acute oral exposure in rats clinical symptoms such as discoloured urine, soft and discoloured faeces and anogenital soiling were noted at 200 mg/kg bw. At higher doses ptosis (at 300 mg/kg bw) and salivation, lethargy, piloerection, prone, unkempt appearance, dark faeces and a wasted appearance (at 500 mg/kg bw) were noted in addition. These effects were transient in nature. Clinical signs were apparent from 1 hour after dosing. Recovery was completed by Day 4 (200 mg/kg bw) to Day 9 (500 mg/kg bw). At 2000 mg/kg bw all rats died (time of death after dosing: between 2 hrs and 2 days). These animals showed clinical signs such as yellow-red chromaturia, loose stools, compound-coloured faeces, dyspnoea, palpebral closure, piloerection, lethargy, irregular respiration, salivation, ptosis, decrease in locomotor activity, soiled fur in the anogenital region and prone position. The majority of surviving rats dosed at 200 mg/kg bw failed to gain body weight during the firsts week of the observation period. Rats treated at 500 mg/kg bw lost large amounts of body weight between Day -1 and Day 8.

All surviving rats did gain body weight between Day 8 and 15, and all rats treated at 200 mg/kg bw and the female treated at 500 mg/kg bw gained overall body weight during the observation period. Macroscopic changes were noted in one male treated at 500 mg/kg bw (enlarged kidneys). Examination of decedents treated at 500 or 2000 mg/kg bw revealed abnormal contents (orange fluid) in the stomach and small intestine of three rats. In one rat dosed at 2000 mg/kg bw abnormal contents were also found in the large intestine and caecum and the caecum was also found to be thin. The mucosal surfaces of the stomach were also orange in two individuals treated at 2000 mg/kg bw. Dark contents were apparent in the stomach and jejunum of one rat treated at 2000 mg/kg bw. The mucosal surface of the stomach of this rat was also dark. In two rats the connective tissue in the abdominal cavity was yellow. One male treated at 500 mg/kg bw had dark contents of the bladder and a female had dark areas on the lungs (RAR Vol. 3, B.6.2./01-02)

Following acute dermal administration in rats at the dose level of 2000 mg/kg bw no adverse clinical signs were noted. Principal signs of reaction to treatment were staining of the snout noted from 30 minutes or 1 hour after dosing and orange coloured urine apparent from Days 2 and 4. Recovery of rats as judged by external appearance and behaviour, was complete by Day 5. Slight erythema affecting two females between Days 4 and 9 and orange staining throughout the observation period. During the first week of the observation period the majority of animals lost body weight, failed to gain body weight or achieved only modest body weight gains. All rats gained weight between Day 8 and day 15. However, one male failed to regain its pre-study body weight and the body weight gain in some individuals was only modest. No macroscopic changes were observed in animals killed on Day 15 (RAR Vol. 3, B.6.2.2/01)

Following acute inhalation administration in rats at a concentration of 0.79 mg/L (4 hrs, whole body) no deaths were observed. Abnormal body posture, abnormal respiratory pattern and rubbing of the snout or paws against the mesh of the exposure compartment were observed in a proportion of rats exposed to quinoclamine. These signs were considered to be consistent with the response to exposure to an irritant dust. A lesion involving the cornea (keratitis) and resulting in some opacity in the eye was evident, in a proportion of rats exposed to the test substance, from Day 2 of the observation period. This sign persisted, particularly in females, during the entire observation period. There was also a marked decrease of bodyweight over a period of 5 days following exposure to quinoclamine. Subsequently the rate of bodyweight gain was similar to or in excess of that observed for the control rats. Furthermore, there was a marked to moderate reduction in food consumption for 6 days in male rats and for 7 days in female rats following exposure to quinoclamine, and water consumption was reduced for 2-7 days following exposure. Following changes were observed during the necropsy: penis was inflamed and of swollen appearance in 2 male rats exposed to quinoclamine, and the fur and tail of all exposed rats were stained orange. The study was conducted according to GLP but the study was considered not acceptable for the purpose of classification for acute toxicity due to low amount of respirable particles (about 40% by weight of the test substance in the chamber air was 5.5 µm or less) (RAR Vol. 3, B.6.2.3/01).

# **2.6.2.10.2** Comparison with the CLP criteria regarding STOT SE (specific target organ toxicity-single exposure)

Specific target organ toxicity (single exposure) is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance, which are not covered by the other hazard classes. STOT SE should be considered where there is clear evidence of toxicity to a specific organ especially when it is observed in the absence of lethality. The hazard class STOT SE is differentiated into STOT SE Category 1 and 2; and STOT SE Category 3.

Classification in STOT SE 1 is required for substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure. Substances are classified in this category on the basis of reliable and good quality evidence from human cases or epidemiological studies, or observations from animal studies in which significant and/or severe toxic effects of relevance to human health are seen at generally low exposure levels (Annex I: Table 3.8.1 of the CLP Regulation).

Classification in STOT SE 2 is required for substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure. Substances are classified in this category on the basis of observations from animal studies in which significant toxic effects of relevance to human health are seen at generally moderate exposure levels (Annex I: Table 3.8.1 of the CLP Regulation).

In the acute toxicity studies performed in the rat, no specific target organ toxicity were noted which were not covered by the other hazard classes. Following acute oral administration, abnormal contents (such as coloured fluids) were noted in the stomach, intestine and caecum. Furthermore, enlarged kidney (one male), small intestine (three females), and dark areas of the lungs (one female) were noted following acute oral administration. These effects were however, not considered of concern for a classification as STOT-SE since the effects were noted at doses with the presence of lethality.

Classification in STOT SE 3 is limited to transient narcotic effects and respiratory tract irritation (Annex I: Table 3.8.1 of the CLP Regulation).

The criteria for respiratory tract irritation (RTI) include "*There are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation" (Annex I: 3.8.2.2.1 of the CLP Regulation). The criteria for narcotic effects include "Narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 specific target organ toxicity single exposure" (Annex I: 3.8.2.2.2 of the CLP Regulation).* 

There were no specific respiratory tract irritant or narcotic effects observed for quinoclamine that are indicative of STOT SE 3 classification.

# 2.6.2.10.3 Conclusion on classification and labelling for STOT SE (specific target organ toxicity-single exposure)

No classification for STOT SE is proposed for quinoclamine.

#### 2.6.3 Summary of repeated dose toxicity (short-term and long-term toxicity)

#### Specific target organ toxicity-repeated exposure (STOT RE) 2.6.3.1

(specific target organ toxicity - repeated exposure)						
Method, guideline, deviations if	Test substance, route	Results	Reference			
any, species, strain, sex, no/group	of exposure, dose	- NOAEL/LOAEL				
	levels, duration of	- target tissue/organ				
	exposure	- critical effects at the LOAEL (bold text)				
Oral 28-day study	Quinoclamine (purity:	<u>5 ppm:</u>	RAR Vol. 3,			
	00.00()		D ( 2 1 1/01			

Table 2.6.3.1-1. Summary table of animal studies on repeated dose toxicity (short-term and long-term toxicity) STOT RE

	levels, duration of exposure	<ul> <li>target tissue/organ</li> <li>critical effects at the LOAEL (bold text)</li> </ul>	
Oral 28-day study	Quinoclamine (purity:	<u>5 ppm:</u>	RAR Vol. 3,
	99.0%)	No treatment related effects	B.6.3.1.1/01
OECD TG 407			
	Oral (dietary)	<u>50 ppm:</u>	Anonymous
Rat		No treatment related effects	15 (2002)
	0, 5, 50, 500, 1000		
Crl:CD <sup>®</sup> (SD)IGSBR	ppm (corresponding to	<u>500 ppm:</u>	Report No.:
	0, 0.5, 4.7, 44 and 84	↓ <b>bw gain</b> (M:19%, F:21%, n.s)	619/148
M, F	mg/kg bw/day for	$\downarrow$ FC (F)	
	males; 0, 0.5, 5.3, 48	-changes in haematological parameters	New data for
5/sex/dose	and 90 mg/kg bw/day	(↓haemoglobin (M:10%), ↓red blood cell	the Annex I
	for females)	count (M), ↓packed cell volume	renewal: No
		(M),↑reticulocytes (M),↑absolute	
Deviations from OECD TG 407:	28 consecutive days	reticulocytes (M), <sup>†</sup> red cell distribution width	
Detailed clinical observations and		$(M, F)$ , $\uparrow$ haemoglobin distribution width $(M, $	
functional observations were not		F))	
made, oestrus cycle of females was		-changes in biochemistry (1alanine	
not determined, determinations of		aminotransferase (M), ↑bilirubin (M, n.s., F,	
haematocrit and blood clotting		n.s.))	
time/potential were not included in		-changes in urine analysis parameters (red-	
the haematological examinations,		, brown- or dark coloured urine (M, F),	
thyroid hormones were not		↑amorphous debris (M, F), ↑urine volume	
investigated, seminal vesicles were		(M))	
not weighed, cervix was not		-changes in organ weights (1) thymus,	
preserved for histopathological		(adjusted) M: 25%, F: 41%)	
examination		-histopathological changes in the kidneys	
		(†eosinophilic hyaline droplets in the	
GLP: Yes		cytoplasm of the proximal tubular	
		epithelium) (M)	
		1000 ppm:	
		$\frac{1}{1000}$ <b>by gain</b> (M: 42%, F: 41%)	
		LFC (M, F)	
		-changes in haematological parameters	
		(1 haemoglobin (M: 8%, F: 13%), 1 red blood	
		cell count (M, F), \packed cell volume (M,	
		n.s, F), reticulocytes (M, F), absolute	
		reticulocytes (M, F), red cell distribution	
		width (M, F), <i>haemoglobin</i> distribution	

	-		r
		width (M, F), $\uparrow$ mean platelet volume (M),	
		↑platelet distribution width (M),	
		↑prothrombin time (M), activated partial	
		thromboplastin time (M),↑plateletcrit (F),	
		↑platelet (F))	
		-changes in biochemistry (Jalanine	
		aminotransferase (M),↑bilirubin (M, n.s., F,	
		S.S.))	
		-changes in urine analysis parameters	
		(red-, brown- or dark coloured urine (M,	
		F), amorphous debris (M, F), urine volume	
		(NI))	
		-changes in organ weights ( $\downarrow$ urymus M.	
		-macrosconical changes (large kidney one	
		male only <sup>a</sup> )	
		-histopathological changes in the kidneys	
		(teosinophilic hvaline droplets in the	
		cytoplasm of the proximal tubular	
		epithelium, minor papillitis characterized by	
		hyperbasophilia of the collecting duct	
		epithelium, interstitial polymorph	
		accumulation and hyperplasia of the	
		urothelium overlying the renal papilla) (M)	
		NOAEL (both sexes): 50 ppm (corresponds	
		to 4.7 and 5.3 mg/kg bw/day in males and	
		females, respectively)	
		LOAEL (both sexes): 500 ppm (corresponds	
		to 44 and 48 mg/kg bw/day in males and	
		females, respectively)	
Orel 28 descetador		2	DAD V-1 2
Oral 28-day study	Quinociamine (purity:	<u>3 mg/kg bw/day:</u>	KAK VOI. 5, D $\leq 2.1.2/01$
No guidalina statad in study raport	99.0%)	No treatment-related effects	D.0.3.1.2/01
No guidenne stated in study report	Oral	10 mg/kg bw/day:	Anonymous
Dog	(cansules)	-clinical signs (red- or black coloured urine	16(2002)
Dog	(eupsuies)	(F))	10 (2002)
Beagle	0 3 10 30 100 <sup>b</sup>	-changes in urinalysis parameters (^turbidity	Report No ·
Dougle	mg/kg bw/day	(M))	619/149
M. F			
	28 consecutive days	30 mg/kg bw/day:	New data for
1/sex/dose		<b>clinical signs</b> (red- or black coloured urine	the Annex I
		(M, F))	renewal: No
		↓FC	
The study report was checked for		-changes in urinalysis parameters	
compliance with OECD TG 409		(↑turbidity (M))	
adopted 21st September 1998 and		-organ weight changes (↑abs spleen (M:	
the following deviations were		89%, F: 51%), rel spleen (M: 97%, F: 58%))	
observed:		-histopathological changes (kidneys: tubular	
<i>i. Four weeks treatment instead of 3</i>		nephropathy and transitional cell hyperplasia	
months		(M, F); urinary bladder: transitional cell	
11. The group size (2 animals) is		nyperplasia (M, F))	
11 .1 .1.(0			
smaller than recommended (8		100 <i>d</i> 1 /1 b	
smaller than recommended (8 animals- four females and four		100 mg/kg bw/day <sup>b</sup> :	
smaller than recommended (8 animals- four females and four males).		<u>100 mg/kg bw/day<sup>b</sup>:</u> - <b>clinical signs</b> (red- or black coloured urine	
smaller than recommended (8 animals- four females and four males). iii. Haematocrit was not determined iv. No optical englished englished		<u>100 mg/kg bw/day<sup>b</sup>:</u> - <b>clinical signs</b> (red- or black coloured urine (M, F), vomiting (M, F), subdued on Day 3 (F))	
smaller than recommended (8 animals- four females and four males). iii. Haematocrit was not determined iv. No ophtalmological examination was performed		<u>100 mg/kg bw/day<sup>b</sup>:</u> - <b>clinical signs</b> (red- or black coloured urine (M, F), vomiting (M, F), subdued on Day 3 (F)) <b>bw loss</b> (Day 4: 13% (M), 18% (F))	
smaller than recommended (8 animals- four females and four males). iii. Haematocrit was not determined iv. No ophtalmological examination was performed v. Ornithine decarboxylase was not		<u>100 mg/kg bw/day<sup>b</sup>:</u> - <b>clinical signs</b> (red- or black coloured urine (M, F), vomiting (M, F), subdued on Day 3 (F)) ↓ <b>bw loss</b> (Day 4: 13% (M), 18% (F)) - <b>neor food consumption</b> (M, F)	
smaller than recommended (8 animals- four females and four males). iii. Haematocrit was not determined iv. No ophtalmological examination was performed v. Ornithine decarboxylase was not determined		100 mg/kg bw/day <sup>b</sup> : -clinical signs (red- or black coloured urine (M, F), vomiting (M, F), subdued on Day 3 (F)) ↓ <b>bw loss</b> (Day 4: 13% (M), 18% (F)) -poor food consumption (M, F) -changes in biochemistry (Day 4:  sodium	
smaller than recommended (8 animals- four females and four males). iii. Haematocrit was not determined iv. No ophtalmological examination was performed v. Ornithine decarboxylase was not determined vi. Gallbladder and thymus were not		100 mg/kg bw/day <sup>b</sup> : -clinical signs (red- or black coloured urine (M, F), vomiting (M, F), subdued on Day 3 (F)) ↓ <b>bw loss</b> (Day 4: 13% (M), 18% (F)) -poor food consumption (M, F) -changes in biochemistry (Day 4: ↓sodium (M, F),  notassium (M, F),  chloride (M, F)	

	r	r	r
vii. Histopathological examination		$\uparrow$ urea (M, F), $\uparrow$ total bilirubin (M, F),	
was limited to following organs:		$\uparrow$ creatinine (M, F), $\uparrow$ total cholesterol (M, F))	
kidney, liver, urinary bladder		-organ weight changes ( <i>†</i> abs liver (M: 11%,	
		F: 20%), ↑rel liver (M: 51%, F: 44%), ↑abs	
GLP: Yes		spleen (11%, F: 20%), ↑rel spleen (M: 45%,	
		F: 320%), ↑abs kidney (M, 17%, F: 15%),	
		↑rel kidney (M: 60%, F: 38%)	
		-macroscopical changes (abnormal urinary	
		bladder contents) (F)	
		-histopathological changes (kidneys: tubular	
		nephropathy and transitional cell hyperplasia	
		(M F): urinary bladder: transitional cell	
		hyperplasia and arteritis (M E) and epithelial	
		nyperplasia and alternas $(W, T)$ and epithematic necrosis $(M)$	
		Study accepted as a range finding study only	
		Due to limited historythology and low	
		number of animals used it is not appropriate	
		to optablish a NOAEL/LOAEL The results of	
		the studies and cousidered cousine call for	
		ine siuay are considered equivocal for	
		classification.	DAD V 1 2
Oral 90-day study	Quinociamine (purity:	50  ppm:	RAK VOI. 3,
NT 111 4 4 1 4 1	not stated in study	$\downarrow FC (F: 12\%)$	B.0.3.2.1/01
No guideline stated in study report	report)	water consumption (15%) (F)	A
	$O(1/\Gamma)$	-changes in biochemistry	Anonymous
D (	Oral (dietary)	$(\downarrow Albumin/Globulin ratio (M, F))$	17 (1972)
Rat	0.50.000 1.1000	-organ weight changes (Trel mandibular	D (N
	0, 50, 200 and 1000	gland M: 27%, n.s.))	Report No.:
Sprague-Dawley (SPPF)	ppm (equivalent to 0,	200	not specified
	3, 14, 62 mg/kg bw	<u>200 ppm:</u>	N. 1. C
M, F	day in males and $0, 3,$	$\downarrow$ bw gain (M: 6%)	New data for
<i></i>	13, 65 mg/kg bw day	$\downarrow$ FC (F: 11%)	the Annex I
5/sex/dose	in females)	↓water consumption (12%) (F)	renewal: No
		-changes in biochemistry	
The study report was checked for	13 weeks	(↓Albumin/Globulin ratio (M))	
compliance with OECD TG 408		-organ weight changes (frel left adrenal (M:	
adopted 21st September 1998 and		<b>60</b> %), $\uparrow$ rel mandibular gland (M: 27%), $\uparrow$ rel	
the following deviations were		right kidney (M: 7%))	
observed:		-histopathological changes in spleen	
<i>i.</i> Housing and feeding conditions		(themosiderin deposition (M, F) and kidney	
are not reported		(hyaline droplets in the cortical epithelium	
ii. Few animals were used in the		(M))	
study, 5/sex/dose (the guideline			
recommends 10/sex/dose)		<u>1000 ppm:</u>	
iii. It is not indicated in the study if		$\downarrow$ bw gain (F: 7%)	
detailed clinical observations were		↓FC (M: 5%, F: 14%)	
made		↓water consumption (M: 23%, F: 17%)	
iv. No ophthalmological		-changes in biochemistry	
examination was made		(↓Albumin/Globulin ratio (M), ↑GOT (M,	
v. Sensory reactivity to stimuli of		n.s.))	
different types and functional		-organ weight changes (↑abs spleen	
observations were not made.		(M:58%, F: 18%), ↑rel spleen (M: 63%, F:	
vi. Haematological examinations		35%), ↑abs liver (M: 12%), ↑rel liver (M:	
were limited (erythrocyte count,		16%, F: 19%), †abs kidney (M: 20%), †rel	
platelet count and measure of blood		kıdney (M: 11%, F: 17%), ↑rel left adrenal	
clotting time/potential was not		$(M: 80\%)$ , $\uparrow$ rel mandibular gland $(M: 40\%)$ )	
included)		-histopathological changes in spleen	
vii. Biochemical determinations		( $\uparrow$ hemosiderin deposition (M, F), liver (bile	
were limited (sodium, potassium,		duct proliferation (M, F), in kidney (hyaline	
glucose, total cholesterol, urea,		droplets in the cortical epithelium (M))	
blood, urea nitrogen, creatinine			
were not included)		NOAEL (both sexes): 50 ppm (corresponds	
viii. Urinalysis were limited		to to 3 mg/kg bw/day)	
(appearance, volume, osmolality,			

glucose and blood/blood cells were not included) ix Pituitary, parathyroid, thymus, oesophagus, trachea, aorta, uterus, female mammary gland, prostate, urinary bladder, peripheral nerve, skin and eyes were not preserved for histopathological examination x. No historical control data available		LOAEL (both sexes): 200 ppm (corresponds to 14 and 13 mg/kg bw/day in male and females, respectively) Study considered limited and accepted as supportive data only	
GLP: No			
Oral 90-day study OECD 408 (1998) Rat Cr1:CD (SD)IGSBR M, F 10/sex/dose GLP: Yes	Quinoclamine (purity: 99%) Oral (dietary) 0, 50, 200 and 800 ppm (equivalent to 0, 3.61, 13.89, 56.74 mg/kg bw/day in males, and 0, 4.56, 17.81, 74.81 mg/kg bw/day in females) 13 weeks	50 ppm:         -clinical signs (†fur staining) (M, F)         ↓ bw gain (Start to week 13: F 17%)         ↓ FC (F, n.s.)         ↑ hypoactivity and hyperactivity (at start of treatment) (M, F)         -changes in biochemistry (↑mean alanine aminotransferase (M))         200 ppm:         -clinical signs (↑fur staining) (M, F)         ↓ bw gain (Start to week 13: F 21%)         ↓ FC (F)         ↑ hypoactivity and hyperactivity (at start of treatment) (M, F)         -changes in myelogram data (↓mean in eosinophils (F)↓ total myelopoietic cells (F))         -changes in haematological parameters (↑haemoglobin distribution width (M, F), ↑ reticulocytes (M, F), ↑ abs reticulocytes         (F), ↓ red blood cell count (M, F), ↓ packed cell volume (F), ↓ haemoglobin (F: 4%), ↑ activated partial thromboplastin time (M))         -changes in urinalysis (dark straw coloured urine (M, F))         -changes in organ weights (↑rel spleen (M: 22%), ↑rel liver (F: 11%), ↓ rel thymus (F: 41%))         -histopathological changes in spleen (M: 22%), ↑rel liver (F)), in liver (sinusoidal cell pigment (M, F)), in kidneys (↑extent of eosinophilic hyaline droplets in the cytoplasm of the proximal tubular epithelium (M)), in thymus (minor thymic atrophy (M, F))         800 ppm:         -clinical signs (↑fur staining) (M, F)         ↓ bw gain (M: 20-28%, F: 27-38%)         ↓ FC (M, F)         ↑hypoactivity and hyperactivity (at start of treatment) (M, F)	Vol. 3, B.6.3.2.1/02 Anonymous 18 (2003) Report No.: 0619/132 New data for the Annex I renewal: No
		(↑red cell distribution width (M, F), ↑haemoglobin distribution width (M, F), ↑mean cell volume (F), ↑reticulocytes (M, F),	

	<b>r</b>	r	r
		↑abs reticulocytes (M, F), ↓packed cell	
		volume (M, F), $\downarrow$ red blood cell count (M, F),	
		haemoglobin (M: 10% F: 11%) factivated	
		partial thrombon lastin time (M) Inlatelet	
		distribution solida (M) + many soli	
		distribution width ( $NI$ ), $\downarrow$ mean cell	
		haemoglobin (F))	
		-changes in biochemistry (↑mean aspartate	
		aminotransferase (M), ↑mean alanine	
		aminotransferase (M, n.s.))	
		-changes in uringlysis (dark straw coloured	
		-changes in urmarysis (dark shaw coloured	
		urine (M, F))	
		-changes in organ weights (frel spleen (M:	
		44%, F: 22%), ↑rel liver (M: 10%, F: 16%),	
		↑brain (M), ↓rel thymus (F: 48%))	
		-macroscopic changes (enlarged spleen two	
		males)	
		-nistopathological changes in spieen	
		( $\uparrow$ incidence of congestion (M, F), $\uparrow$ extent of	
		haemopoiesis (M), ↑extent of pigment (F)),	
		in liver (sinusoidal cell pigment (M, F)), in	
		kidneys (1 extent of eosinophilic hyaline	
		dronlets in the cytonlasm of the proving	
1		tubular onithalium (M) time: 1f	
1		inoutal epimenum (NI), incidence of	
		pigment (F), Textent of focal nephropathy	
		$(M, F)$ , $\uparrow$ papillary interstitial eosinophilia	
		(two males)), in thymus (thymic atrophy (M,	
		F))	
		NOAFL (E): not established	
		NOAEL (I): not established	
		NOAEL (M): 50 ppm (corresponds to 5.61	
		mg/kg bw/day)	
		LOAEL (F): 50 ppm (corresponds to 4.56	
		mg/kg bw/day)	
		I O AFL (M): 200 ppm (corresponds to 13.89	
		EOALL (W). 200 ppin (corresponds to 15.0)	
		mg/kg bw/day)	
Two generation reproduction study	K-1616	<u>1 ppm:</u>	RAR Vol. 3,
	(Quinoclamine)	Parental:	B.6.6.1/01
In-house method		-clinical signs (hunched posture F0/F1)	
	Purity: 98.5%	1 + 1 + 1 + 1 + 2 + 1 + 1	Anonymous
Rat		$\downarrow$ DW (P1 M: 5%; P2 M: 7%; P2 F 4%)	19 (1975)
	0 1 25 500 mm	$\downarrow$ bw gain (P1 M·4% P2 M·11%·P2 F·	17 (1713)
Same and Develop	0, 1, 23, 500 ppin	40/)	Dement M
Sprague-Dawley	Corresponding to:	4%)	Keport No.:
1	F0: 0, 0.07, 1.6, 30.9		854-111
M, F	mg/kg bw/day in	Offspring:	
1	males; 0, 0.08, 1.9 and	-increased incidence of gray lung cysts in	New data for
25/sex/group	37.7 mg/kg hw/day in	F2b offspring reared for 3 months (18	the Annex I
B.o.P	females	compared to 11 in control group)	renewal: No
1	F1.0 0.07 1.7 and	compared to 11 m control group)	renewai. INU
	F1: 0, 0.07, 1.7 and		
Study was checked for compliance	37.0 mg/kg bw/day in	<u>25 ppm:</u>	
with OECD TG 416 (2001) and	males; 0, 0.08, 2.0 and	Parental:	
following deviations were noted:	43.8 mg/kg bw/day in	-clinical signs (hunched posture F0/F1)	
i. No evaluation of the oestrus cycles	females	$b_{W}$ (D1 M· 1%· D2 M· 7%· D2 E 5%)	
was performed for either generation		ψ Uw (I I IVI. 170, F2 IVI. / 70, F2 F 370)	
ii No examination of sperm	The parents of both	↓ bw gain (P1 M: 2%, P2 M: 11%: P2 F:	
n. no communication of sperm	rano parentis or bour	60/	
parameters was performed for either	generations were led	070)	
generation	the appropriate diets		
iii. Gestation length was not	for at least nine weeks	Offspring:	
specified	and then subjected to	-increased incidence of gray lung cysts in	
iv. organs were not weighed	two subsequent	F2b offspring reared for 3 months (29	
v. Vagina, testis, enididymides	mating trials. Fresh	compared to 11 in control group)	
seminal vesicles prostate and	diets were prepared	compared to 11 in control group)	
seminar vesicies, prosidie and	and presents 11-1	500 mm	
coagulating glana were not	and presented weekly		
investigated microscopically	to the rats of all	Parental:	

RMS: SE Co-RMS: DE

	r		
vi. Detailed testicular	generations from	-clinical signs (F0/F1: hunched posture)	
histopathology was not performed	initiation (P1) or	↓ <b>bw</b> (P1 M: 4%; P2 M: 10%; P2 F 10%)	
vii. Postlactational ovary	weaning (F1b—>F2,	<b>by <math>a_{2}</math></b> (D1 M: 70/ D2 M: 110/ D2 E:	
(primordial and growing follicles)	F2b)	↓ <b>DW gain</b> (P1 M: 7%, P2 M: 11%; P2 F:	
histopathology was not performed		9%)	
viii. For the offspring, age at vaginal		$\downarrow$ <b>litter size</b> in F2a and F2b generations	
opening or PPS for the F1 and F2		(mean litter size born in F2a generation: 4	
was not aeterminea		males and 5 females compared to 6 males	
CLP: No		and 6 females in the control group; mean	
GEI: NO		litter size born in F2b generation: 5 males	
		and 5 females compared to 7 males and 6	
		females in control group)	
		<u>Offspring:</u>	
		offenring)	
		onsping)	
		$\downarrow$ <b>bw</b> during lactation (F1a: 13% and 7% in	
		males and females, respectively; F1b: 14%	
		and 9% in males and females, respectively;	
		F2a: 8% and 9% in males and females,	
		respectively; F2b: 11% and 5% in males and	
		remaies, respectively)	
		$\downarrow$ <b>litter size</b> in F2a and F2b generations	
		(mean litter size born in F2a generation: 4	
		males and 5 females compared to 6 males	
		and 6 females in the control group; mean	
		litter size born in F2b generation: 5 males	
		and 5 females compared to 7 males and 6	
		increased incidence of anothing system	
		-Increased incluence of gray lung cysts in E2b offenring reared for 2 months (20	
		compared to 11 in control group)	
		compared to 11 in control group)	
		NOAEL parental and offsprings: 25 ppm (1.6	
		mg/kg bw/day)	
		NOAEL reproductive toxicity: 500 ppm (37	
		mg/kg bw/day)	
Oral 90-day study	Quinoclamine (purity:	<u>3 mg/kg bw/day:</u>	Vol. 3,
0000 (1000)	99%)	-clinical signs (coloured urine and faeces)	B.6.3.2.2/01
UECD 409 (1998)	Orel (2017-1-1)	(M, F)	A.m. or
Dog	Oral (capsules)	10 mg/kg bw/dag:	Anonymous
Beagle	0 3 10 and 30 mg/kg	-clinical signs (coloured urine and faeces)	20 (2002)
Dougio	bw/dav	(M, F)	Report No.:
M, F	· · · · · · · · · · · · · · · · · · ·	<b>bw gain</b> (F: 12% n.s.)	0619/134
	13 weeks	↓FC (M)	
4/sex/dose		-changes in haematological parameters	New data for
		(↓red blood cell count (M, F), ↑reticulocyte	the Annex I
GLP: Yes		count (M, F), ↓mean cell haemoglobin	renewal: No
		concentration (M, F), $\uparrow$ platelet count (F, n.s.),	
		$\uparrow$ platelet crit (F, n.s.), $\uparrow$ total white blood cell	
		count (F, n.s.))	
		-cnanges in organ weights (fadjusted liver	
		$(1^{\circ}, 2770)$ , [aujusted myroid/paratnyroid (M: 33%))	
		-histopathological changes in hone marrow	
		(haemopoiesis (M, F)), liver (sinusoidal cell	
		pigment characterised by presence of	
		intracytoplasmic iron-containing pigment (M.	
		F)), <u>urinary bladder (cystitis (one female))</u>	

		30 mg/kg hw/day:	
		-clinical signs (coloured urine and faeces)	
		(M, F)	
		↓ <b>bw gain</b> (M: 31%, F: 35%)	
		↓FC (M, F) changes in haematological parameters	
		(Ired blood cell count (M. F), Ihaemoglobin	
		$(M: 18\%, F: 19\%)$ , $\downarrow$ packed cell volume (M,	
		F), ↑reticulocyte count (M, F), ↓mean cell	
		haemoglobin concentration (M, F), ↑mean	
		cell volume (M, F), $\uparrow$ platelet count (M, F), $\uparrow$ platelet arit (M, F), $\uparrow$ total white blood call	
		(M, F), (total white blood cent count (M, F))	
		-changes in biochemistry (↑mean total	
		bilirubin (M, F))	
		-changes in organ weights (†adjusted liver	
		(M: 20%, F: 29%), [adjusted thyroid/parathyroid (M: 32%) fadjusted	
		spleen (F: 56% n.s.))	
		-macroscopic changes in spleen (enlarged	
		two females), liver (mootled, one female) and	
		urinarybladder (red, one female)	
		- <b>instopathological changes</b> in <u>bone marrow</u> (haemonoiesis characterised by greater	
		cellularity (M, F)), spleen (haemopoiesis	
		characterised by increased haemopoietic cells	
		in the red pulp (M, F), congestion of the	
		splenic red pulp (M, F)), <u>liver</u> (sinusoidal cell	
		intracytoplasmic iron-containing pigment (M.	
		F), bile duct hyperplasia (M, F)), <u>kidney</u>	
		(pigment (M, F)), urinary bladder	
		(transitional cell hyperplasia (M, F), arteritis	
		(one male), cystitis (one female))	
		NOAEL (both sexes): 3 mg/kg bw/day	
		LOAEL (both sexes): 10 mg/kg bw/day	
Oral 2-year study	Quinoclamine (purity:	<u>2 ppm:</u>	Vol. 3,
In house method	98.5%)	No treatment-related effects	B.6.3.3.1/01
in nouse method	Oral (dietary)	10 ppm:	Anonymous
Dog		↓bw (M: week 52: 5%, week 104: 12%; F:	21 (1976)
Beagle	0, 2, 10, 50, 250 and	week 104: 19%)	
ме	1000 ppm (equivalent to $0.066, 0.32, 1.42$	$\downarrow$ bw gain (Week 0-52: M: 2.4% compared to 0.3% in controls E: 3% compared to 1.7% in	Report No:
191, 1	7.62  and  26.6  mg/kg	controls: Week 52-104: M: 0.3% compared	034/110
4/sex/dose	bw/day in males, and	to 1.2% in controls, F: 0.3% compared to	
	0, 0.06, 0.31, 1.39,	1.5% in controls)	New data for
GLP: Yes	6.79 and 29.1 mg/kg	-haematological changes (Jerythrocytes (F:	the Annex I
The study is acceptable. It was	ow/day in temales)	week 104) -macrosconical changes in urinary bladder	renewai: No
checked for compliance with OECD	2 year	(mucosa brown or tan in colour in 2 of 6	
TG 409 and the following deviations		animals)	
were noted:			
1. Study duration 2-years instead of		<u>50 ppm:</u> hw (M: week 52: 3%, week 104: 8%, E.	
ii. Housing conditions is not		week 52: 2%, week 104: 5%)	
presented in the study report		$\downarrow$ bw gain (Week 0-52: M: 2.6% compared to	
iii. Ornithine decarboxylase, gamma		2.4% in controls, F: 2.3% compared to 1.7%	
glutamyl transpeptidase, urea		in controls; Week 52-104: M: $0.1\%$	
niirogen, blood creatinine and		compared to 1.2% in controls, F: 0.9%	
seram protein were not included in	1	compared to 1.5% in conduits)	

the clinical biochemistry	-changes in haematological parameters	
examination	$\downarrow$ haematocrit (M, Week 76), $\downarrow$ erythrocytes	
iv. No ophthalmological	(M Week 76, F Week 104)	
examination performed	-macroscopical changes in <u>ovary</u> (one small	
v. The following tissues were not	in size), <u>urinary bladder</u> (mucosa brown or	
included in the histopathology	tan in colour), <u>spleen</u> (dark in colour or	
investigation: peripheral nerve,	margins dark))	
uterus, eyes ana spinat cora.	- <b>instopathological changes</b> in <u>luing (local</u>	
	macrophages (one female), hile plugs in	
	canaliculi (one female)) urinary bladder	
	(pigment in mucosal cells (M,F))	
	(1.2	
	250 ppm:	
	-clinical signs (brown-tined urine)	
	↓bw (week 104: M: 8%, F: 6%)	
	↓ <b>bw gain or bw loss</b> (week 0-52: M: 1.9%	
	compared to 2.4% in controls, F: 2%	
	compared to 1.7% in controls, week 52-104:	
	M: -0.1% compared to 1.2% in controls, F:	
	0.1% compared to 1.5% in controls)	
	-changes in haematological parameters	
	$(\downarrow$ haemoglobin (M: Weeks 26: 16%, 52:	
	17%, 76: 12%; F: 26: 16%, 76: 20%),	
	$\downarrow$ naematocrit (M: weeks 26, 52, 76; F:	
	Weeks 26, 70, 104), $\downarrow$ erythrocytes (M: Weeks 26, 52, 76, 104); E: Weeks 76, 104);	
	$\sim$ changes in biochemistry: ( $\uparrow$ serum	
	glutamic-nyruvic transaminase (M F)	
	↑alkaline phosphatase (M, F),↑serum	
	glutamic-oxaloacetic transaminase (M, F))	
	-macroscopical changes in <u>urinary bladder</u>	
	(mucosal surface brown or yellow-gray),	
	liver (brown in colour, rough surfaced, tough	
	in consistency, firm), spleen (dark in colour	
	or margins dark), kidneys (depressed areas	
	on surface), <u>ovary</u> (cyst on one), <u>lung</u> (white	
	foci on surface)	
	- <b>nistopathological changes</b> in <u>adrenal</u>	
	( vacuolation of conteal cens (ivi,i'), local	
	(foci of foamy macronhages (M F)) spleen	
	(extramedullary haematopoesis (F).	
	congestion (F)), liver (pigment in cytoplasm	
	of hepatocytes and kuppfer cells (M,F),	
	pigment in macrophages (F), periportal	
	fibrosis (M,F), bile duct proliferation (M,F),	
	bile plugs in canaliculi (one female),	
	sinusoidal distension (F)), kidney (tubular	
	nephrosis (one female), <u>urinary bladder</u>	
	(pigment in mucosal cells (M,F), pigment	
	raden macrophages (F))	
	1000 ppm:	
	-mortality (one of each sex sacrificed in	
	extremis during week 65)	
	-clinical signs (brown-tined urine, orange	
	stained hair around urogenital area, during	
	the second year of study: pale appearing oral	
	mucosal membranes, yellowish discoloration	
	of the eyes and thinness in the female	
	sacrificed in extremis, and unhealthy	

appearance characterized by thinness and
lethargy in the male sacrificed in extremis)
↓ <b>bw</b> (week 52: M: 21%, F:26%; week 104:
M: 23%, F: 33%)
<b>bw gain or bw loss</b> (Weeks 0-52: M: 0.3%)
compared to 2.4% in controls. F:
-0.6% compared to 1.7% in controls:
Weeks 52-104: M: 0.1% compared to 1.2%
in controls $F: -0.6\%$ compared to 1.5% in
controls)
-changes in haematological narameters (all
nost treatment intervals: haemoglobin M: un
to 26% E: up to $47\%$ [haematocrit (M E)
exythrocytes (M E):  the state of the counts (F:
Week 104)
changes in biochemistry: (Aserum
-changes in biochemistry. ( serum
giutanne-pyruvie transammase ( $W$ , $F$ ), Aphralina mhaamhataaa ( $M$ , $E$ ), Aphraim ( $E$ )
Vacha 52, 78) Asserve slutenings
weeks 52, 78), [seruin glutamineo-
oxaloacetic transaminase (M, F))
-changes in organ weights: F:  rel lungs
$(92\%)$ (F), $\uparrow$ rel spleen (77%) (F), $\uparrow$ rel
gonads (80%) (F), $\downarrow$ rel gonads (55%) M, n.s),
↓rel prostate (45%), n.s))
-macroscopical changes in the liver
(enlarged, lobes thickened and pale, rough
surface and mottled, brown in colour, tough
in consistency, firm), <u>gall bladder</u> (distended,
walls thickened), kidneys (small, depressed
areas on surface, contracted, polycystic-
primarily in the medulla, cortex collapsed,
thickened and opaque areas on capsule),
<u>urinary bladder</u> (brown mucosa or tan in
colour, wall thickened, omentum adhered to
serosal surface), <u>spleen</u> (dark in colour or
margins dark, enlarged), testes (small and
soft), prostate (small at week 52), ovary (cyst
on one), heart (reddish-brown discoloration
at coronary grove, right A/V valve thickened
and vascular with dark raised area near point
of attachment at week 52), lung (raised
yellow gray foci on all lobes, focal
emphysematous appearing areas), cartilage
(yellow to brown in colour), trachea (brown
or gray discoloration), <u>ribs</u> (brown of gray
discoloration), tendons (brown or gray
discoloration), bones (gray in colour),
mesenteric lymph nodes (dark in colour),
small intestine (walls slightly thickened)
-histopathological changes in adrenal
(↑vacuolation of cortical cells (M,F),
necrosis, one female), lung (foci of foamy
macrophages (M,F), focal pneumonitis (M,
F), cholesterol clefts (M,F), fibrosis (one
female), edema (M,F), consolidation (one
male)), <u>spleen</u> (extramedullary
haematopoesis and congestion (M,F)), liver
(pigment in cytoplasm of hepatocytes,
kuppfer cells and macrophages (M.F).
periportal fibrosis (M,F), bile duct
proliferation (M,F), bile plugs in canaliculi
(M.F), sinusoidal distension (F)), kidnev
(tubular nephropathy with fibrosis and renal
tubular regeneration (M.F)), urinary bladder
and a second and a second and a second and a second a sec

		<ul> <li>(pigment in mucosal cells (M,F), edema (one female), pigment laden macrophages (one female)), testis (aspermatogenesis, testicular atrophy, focal nonsuppurative orchitis), ovary (lack of follicle development, follicular cysts (one female), mesenteric lymph nodes (edema, erythrophagocytosis, distension of medullary sinuses (F)), pancreas (edema (F)), gall bladder (hyperplasia (M,F), papillary infolding (M,F), cholelith (one female)), aorta (mineralisation in one female), small intestine (focal enteritis (one female), erosion (one female))</li> <li>NOAEL (both sexes): 10 ppm (corresponds to 0.33 and 0.31 mg/kg bw/day in males and females, respectively)</li> <li>LOAEL (both sexes): 50 ppm (corresponds to 1.42 and 1.39 mg/kg bw/day in males and females, respectively)</li> </ul>	
28-day dermal study OECD 410	Quinoclamine (purity: 99%) Vehicle: 2%	<u>100 mg/kg bw/day:</u> -clinical signs (skin irritation) -macroscopic changes (sores at the treated site) (three females)	RAR Vol. 3, B.6.3.4.1/01
	methylcellulose (w/v)	200 mg/kg hu/dow	22 (2002)
CH:CD:(SD)IGSBR	Dermal	<u>-clinical signs (skin irritation)</u>	Report No ·
M, F	Derman	-changes in biochemical parameters	0619/133
5/sex/dose	0, 100, 300, 1000 mg/kg bw/day	(↓aspartate aminotransferase (F), ↓mean alkaline phosphatase (F n.s.), ↑bilirubin (M	New data for
CI D: Vos	28 dava	n.s.), ↑glucose (M))	the Annex I
OLF. Tes	20 uays	site) (one female)	Tellewal. NO
		1000 mg/kg bw/day:         -clinical signs (skin irritation)         -changes in biochemical parameters         (↓aspartate aminotransferase) (F n.s.), ↓mean         alkaline phosphatase (F), ↑bilirubin (M),         ↑glucose (M))         -changes in urinalysis (dark colour of the         urine) (M, F)         -macroscopical changes (sores at the treated         skin site) (two males)         -histopathological changes in skin         (acanthosis/hyperkeratosis in the epidermis,         subepidermal fibrosis, epidermatitis) and         kidney (tubular degeneration/regeneration)         (one female and one male), hydronephrosis         (one female), pigment (one female))         NOAEL for systemic effects (M, F): 300         mg/kg bw/day         LOAEL for systemic effects (M, F): 1000         mg/kg bw/day         NOAEL local effects (M, F): not estimated	
Long-term toxicity and	ACN technical	4 ppm:	RAR Vol. 3,
carcinogenicity	(Quinociamine)	orange colour) (M, F)	D.0.3.1/01

Oral (dietary)	Purity: 98.3%		Anonymous
cra (dioury)	2 4110 7 9 0.0 70	<u>52 ppm:</u>	23 (1991)
No guideline claims presented in	Carcinogenicity	-changes in urinalysis (yellow/brown or	AV 1/7/00
suuy report	0, 4, 52, 676 ppm	changes in organ weights (Weak 27: $\uparrow$	ARJ/ //90
	corresponding to	kidnev (M· 8%))	New data for
Rat	0, 0.21, 2.82, 37.6	-histopathological changes in <u>urinary</u>	the Annex I
Crl:CD(SD)BR	males and 0, 0.28,	bladder (epithelial hyperplasia (M, F),	renewal: No
	3.65, 49.4 mg/kg	kidneys (epithelial hyperplasis (M, F), ↑	
50/sex/group	bw/day in females	renal focal calcification (F), <u>ureter</u> (epithelial	
The study is acceptable. It was	Chronic toxicology	calcification (M))	
checked for compliance with OECD	groups:		
TG 453 and following deviations were noted:	0, 4, 52, 676 ppm	<u>676 ppm:</u>	
<i>i. Haematological examination was</i>	0.21, 2.89, 38.3 mg/kg	-clinical signs (orange fur staining, $\downarrow$	
not carried out at 3 months (the	bw/day in males; 0,	here gain (terringla an exclusion E 28%)	
guideline recommends measurements at 3 months if effect	0.28, 3.72, 51.5 mg/kg	↓ <b>Dw gain</b> (toxicology evaluation: F: 28%; carcinogenicity evaluation: F: 27%)	
was seen on haematological	e duy in ternates	$\downarrow$ FC (M, F)	
parameters in a previous 90 day	104 weeks	changes in hosmatological nonemators (	
study) ii. Prothromhin time and activated		nacked blood cell volume (M week 27 79. F	
partial thromboplastin time was not		week 53). $\downarrow$ haemoglobin (M: 8% week 27	
investigated		$F 5\%$ week 27 9% week 53) $\downarrow$ red blood	
ui. Urea was not investigated iv. Uterus and epididymides were		cell count (M week 27, 79: F: week 27, 53))	
not weighed		-changes in biochemical parameters ( 1	
v. Coagulating gland, ileum,		blood urea nitrogen (Mns Ens)	
were not investigated for		calcium (M: week 27, 70, $\mathbf{E}$ , $\mathbf{n}$ , $\mathbf{n}$ )	
histopathology		inorganic phosphorous (M: n.s. F: week 27	
		53), $\downarrow$ lactate dehydrogenase (M: week 79.	
GLP: No		103; F: week 103))	
		-changes in organ weights (Week 27: ↑ rel	
		kidney (M: 15%), ↑ adrenals (F: 38%),	
		<u>Week 53</u> : ↑ kidney (M: 10%), Week 79:	
		↑ heart (M: 18%, F: 28%), ↑ brain (F:	
		28%). ↑ spleen (F. 13%). ↑ kidnev (F <sup>.</sup> 19%).	
		Week $104 \cdot \uparrow$ brain (E· 23%) $\uparrow$ thuroid	
		$\frac{\text{reck 104.}}{(\text{E}:420\%)} \uparrow \text{(happed (E: 160\%)} \uparrow \text{-large-le (E)}$	
		(F:45%), + (neart (F: 10%), + adrenais (F:	
		9%),   thymus (F: 50%))	
		orange discoloration (M, F), diuretic animals	
		(M)) -macroscopical changes in urinary bladder	
		(orange discoloration of the urinary bladder	
		serosa) (M, F) and <u>skin</u> (orange staining (M,	
		F)) -histopathological changes in urinary	
		<u>bladder</u> (benign transitional cell papilloma	
		(M, F), epithelial hyperplasia $(M, F)$ polyp	
		kidneys (epithelial hyperplasia (M. F), renal	
		papillary degeneration/necrosis (M, F) $\uparrow$	
		renal cortical scarring (M, F) pelvis polyp	
		(one male), $\uparrow$ renal focal calcification, <u>ureter</u>	

Carcinogenicity study Oral (dietary) No guideline claims in study report Mouse Crl:CD-1 (ICR)BR 50/sex/group The study is acceptable. It was checked for compliance with OECD TG 451 (adopted 7 September 2009). Following deviations were noted: i. the duration of study was 20 months (according to the guideline the duration of the study will normally be 24 months for rodents. Shorter or longer study durations may be used but should be justified). ii. cervix, coagulating gland, Hardian gland and lacrimal gland were not included in the histopathological evaluation. GLP: Yes	ACN technical (Quinoclamine) Purity: 98.57% 0, 3, 30 or 300 ppm (corresponding to averages of 0, 0.38, 3.82 and 40.2 mg/kg bw/day in males and 0, 0.44, 4.48 and 46.4 mg/kg bw/day in females) 80 weeks	<pre>(epithelial hyperplasia (M, F), urethra (epithelial hyperplasia (M, F), <u>adrenals</u> (benign phaeochromocytoma M, F), <u>pancreass</u> (↑ pancreatic acinar atrophy (M, F), <u>parathyroid</u> (epithelial hyperplasia (M), <u>mammary gland</u> (↓ mammary acinar development and secretion (F)), <u>lungs</u> (arterial calcification (M, F), ovaries (lack of cyclic activity)) NOAEL for systemic toxicity (M, F): 4 ppm (corresponds to 0.21 and 0.28 mg/kg bw/day in males and females, respectively) NOAEL for tumour incidence (M, F): 52 ppm (corresponds to 2.82 and 3.65 mg/kg bw/day in males and females, respectively) <u>3 ppm:</u> -clinical signs (orange fur staining) (M, F) -clinical signs (orange fur staining) (M, F) -clinical signs (orange fur staining) (M, F) -clinical signs (orange fur staining) (M, F) -changes in organ weights (↑ rel kidney, M: 14% n.s.) -histopathological changes in <u>adrenal</u> (adrenal spindle cell hyperplasia (F), brown athrophy (F)); <u>stomach</u> (hyperkeratosis and chronic inflammation (F)) <u>300 ppm:</u> ↑ mortality (M, F) -clinical signs (orange fur staining) (M, F) ↓ bw gain (M: 33%, F: 30%) -changes in organ weights (↑ rel liver (F: 20%), ↑ rel kidney (M: 15% n.s., F: 24% n.s.), ↑ rel heart (F), ↑ brain (F)) -histopathological changes in <u>adrenal</u> (↑ adrenal spindle cell hyperplasia (M), brown athropy (F)), <u>kidney</u> (cortical scarring (M, F), hydronephrosis (M, F), <u>liver</u> (chronic inflammation (F), brown pigmentation (F)), <u>sciatic nerve</u> (degeneration (F)), <u>spleen</u> (haemosiderosis (F), <u>heart</u> (generalised periarteritis (F), myocardial fibrosis (13 M, 2 F), <u>stomach</u> (hyperkeratosis (M, F), epithelial hyperplasia (M), dilation of mucosal glands (M, F), <u>lymph nodes</u> (histiocytosis (M, F), <u>lymph nodes</u> (histiocytosis (M, F), <u>lymph nodes</u> (histiocytosis (M, F), <u>lymph nodes</u> (histiocytosis (M, F); <u>3 ppm</u> (corresponding to 0.38 and 0.44 mg/kg bw/day for males and females. respectively)</pre>	RAR Vol. 3 B.6.5.2/01 Anonymous 24 (1993) New data for the Annex I renewal: No
		females, respectively)	

	r	r	<b>T</b>
		LOAEL (M, F): 30 ppm (corresponding to	
		3.82 and 4.48 mg/kg bw/day in males and	
		females, respectively)	
		NOAEL for tumour incidence (F): 30 ppm	
		(4.48 mg/kg bw/day)	
		NOAEL for tumour incidence (M): 300 ppm	
		(40.2  mg/kg hw/day)	
Teratology study	ACN technical	Maternal effects:	RAR Vol 3
formology study	(Quinoclamine)	<u>Muternur erreets.</u>	B 6 6 2 1/02
No guideline claimed in study	(Quinocialinite)	5 mg/kg hw/day:	<b>D</b> .0.0.2.1/02
	Purity: 98.1%	No treatment related effects	Anonymous
Rat			25 (1986)
		20 mg/kg bw/day:	, , , , , , , , , , , , , , , , , , ,
Crl:CD (SD) BR	0, 5, 20 and 75 mg/kg	-macroscopic changes (enlarged spleen, one	Report No .:
	bw/day	dam)	AKJ/4/86
F			
	Vehicle: 0.25% gum	75 mg/kg bw/day:	New data for
24/group	tragacanth	<b>- bw gain</b> (25% day 7-17)	the Annex I
		$\downarrow$ FC (Gestation Days 7-10: 25%, Gestation	renewal: No
GLP: Yes	Gestation Days 7-17	Days $10-13:14\%$ )	
		-macroscopic changes (enlarged spleen	
24/group		4/24 dams)	
The study is acceptable. It was		Developmental effects:	
checked for compliance with OECD		5 mg/kg bw/day:	
IG 414 and following deviations		No treatment-related effects	
i Exposure time in study was once			
daily between days 7 and 17 of		20 mg/kg bw/day:	
pregnancy (the guideline is not		-abnormalities (innominate artery absent,	
intended to examine solely the		one foetus)	
period of organogenesis (e.g. days		-increased incidence of skeletal variants	
5-15 in the rodent) but also effects		(skull: hyoid not ossified; vertebrae: thoracic	
from preimplantation,		centre one or more bilobed)	
when appropriate, through the entire		75	
period of gestation to the day before		<u>/5 mg/kg bw/day:</u>	
caesarean section)		$\downarrow$ foetal weight (7%)	
ii. Treatment was not extended (the		-abnormalities (innominate artery absent,	
guideline states: If preliminary		four foetuses; situs inversus, two foetuses;	
studies, when available, do not		interrupt aortic arch, one foetus)	
indicate a high potential for		-increased incidence of skeletal variants	
preimplantation loss, treatment may		(skull: hyoid not ossified; vertebrae: thoracic	
be extended to include the entire		centre one or more bilobed/bipartite;	
period of gestation, from		sterneorae: 5th and oth sterneorae not	
<i>Fill</i> )		misaligned)	
iii The choice of vehicle was not		misuigneu)	
iustified in study report		NOAEL maternal toxicity: 5 mg/kg bw/day	
		NOAEL developmental toxicity: $5 \text{ mg/kg}$	
GLP: Yes		bw/day	
Teratology study	Quinoclamine	Maternal effects:	RAR Vol. 3.
		5 mg/kg bw/day:	,
No guideline claimed in study	Purity: 99.0%	No treatment-related effects	B.6.6.2.1/04
-			
Rat		20 mg/kg bw/day:	Anonymous
	0, 5, 20, 75 mg/kg	-clinical signs (paddling of the forelimbs	26 (2002)
Crl:CD (SD) IGSBR	bw/day	from Day 14 of gestation)	
l_		↓ <b>bw gain</b> (Days 7-8: 62%, Days 17-19:	Report No.:
F	Vehicle: 1% aqueous	21%)	619/94-
24/	methylcellulose	FC (Days 7-8. 1/0% Days 0 12. 170%	D6154
24/group	Contation D (10)	+10 (Days 7-0. 1470, Days 9-12. 1770,	
	Gestation Days 6-19	Days 12-15: 10%, Days 15-17: 12%,	

The study is accentable. It was	Dave 1	7-18:12%)	New data for
checked for compliance with		(17-17, 1270)	the Annex I
updated OECD TG 414 (2001) and	↓ mea	in gravid dierus weight (15%)	renewal: No
following deviations were noted:	↓ mea	an litter weight (13%)	
i. Exposure time in study was once	75 mg	/lea here/dare	
pregnancy (the guideline is not	-clinic:	al signs (paddling of the forelimbs	
intended to examine solely the	from D	Day 10, nose rubbing)	
period of organogenesis (e.g. days	↓ bw s	gain (Days 17-19: 41%)	
5-15 in the rodent) but also effects	-bw lo	<b>ss</b> (Days 6-7: -4.6 g. Days 7-8: -2.6 g.	
from preimplantation,	Days 8	8-9: -0.4 g)	
when appropriate, through the entire period of gestation to the day before	↓ FC (	(Davs 4-6: 9%, Davs 6-7: 27%,	
caesarean section)	Days 7	7-8: 44%, Days 8-9: 34%, Days 9-12:	
ii. Treatment was not extended (the	30%, I	Days 12-15: 17%, Days 15-17: 13%,	
guideline states: If preliminary	Days 1	17-19: 33%)	
studies, when available, do not	↓ mea	an gravid uterus weight (30%)	
indicate a high potential for preimplantation loss treatment may	↑ post	t-implantation loss (11% compared to	
be extended to include the entire	5% in	control. n.s.)	
period of gestation, from	↑ pur	mber of early intrauterine deaths	
mating to the day prior to scheduled	(11.00	pmpared to 0.7 in control)	
kill)		militten gize (12 commerced to 14.8 in	
iii. The choice of vehicle was not justified in study report	↓ Inea		
justifica în stady report		1)	
GLP: Yes	↓ mea	in litter weight (29%)	
	Develo	opmental effects:	
	<u>5 mg/k</u>	<u>kg bw/day:</u>	
	No trea	atment-related effects	
	20 mg	/ka bw/dav:	
		l weight (7%)	
	↓mean	n litter weight (13%)	
	↑incid	ence of skeletal variations	
	(incom	plete ossification of skull bone	
	(fronta	al and nasal) and unossified fifth	
	sternet	Jiae)	
	75 mg/	/kg bw/day:	
	↓foeta	l weight (12%)	
	↓litter	weight 29%)	
	↑post-	implantation loss (11% compared to	
	5% III ↑pre-ir	mplantation loss (17.4% compared to	
	8.6% i	n control but within current	
	backgr	cound data)	
	↑numb	ber of early intrauterine deaths	
	(1.1 co	ompared to 0.7 in control)	
	↓mean	1 <b>Inter size</b> (12 compared to 14.8 in $1$ )	
	1 tincid	ence of skeletal variations	
	(incom	plete ossification of skull bone	
	(fronta	l and nasal) and unossified fifth	
	sterneb	orae)	
	-malfo	primations (subcutaneous oedema (one	
	foetus	), kidney misshapen (one foetus)	
	hydrop	onephrosis (three foetuses))	
	NOAE	EL maternal: 5 mg/kg bw/day	
	INDAF	L developmental: 5 mg/kg bw/dav	1

Teratology study	ACN (Quinoclamina)	Maternal effects:	DAD Vol 3
Teratology study	ACN (Quinociannie)	2.5 mg/kg bw/day:	B.6.6.2.2/02
No guideline claimed in study	Purity: 98.1%	No treatment-related effects	
D 111			Anonymous
Kabbii New Zealand White	0, 2.5, 7.5, 22.5  mg/kg	<u>7.5 mg/kg bw/day:</u> No treatment-related effects	27 (1986) Report No :
New Zealand White	0w/day	No treatment-related effects	AKJ/3/86
F	Vehicle: 0.25% gum	<u>22.5 mg/kg bw/day:</u>	
	tragacanth	$\downarrow$ bw gain (Day 6-9: 0 kg compared to	New data fpr
16/group	Gestation Dave 6 18	0.08 kg in control, Days 0-28: 5%)	the Annex I
The study is acceptable. It was	Oestation Days 0-18		Tellewal. NO
checked for compliance with		Devialormental effects:	
updated OECD TG 414 (2001) and		2.5  mg/kg bw/day:	
following deviations were noted:		No treatment related effects	
<i>quideline states: If preliminary</i>			
studies, when available, do not		7.5 mg/kg bw/day:	
indicate a high potential for		No treatment-related effects	
preimplantation loss, treatment may		22.5 mg/kg bw/day:	
be extended to include the entire period of gestation from		$\downarrow$ foetal weight (5% n.s.)	
mating to the day prior to scheduled		↑ increased incidence of skeletal variants	
kill)		(increased no. of caudal centra <15 (84 9%)	
<i>ii. During the course of study</i>		compared to 59.9% in control))	
relative number was within the range 54-76% (the guideline		-malformations (scoliosis, one animal,	
recommends the relative humidity		spina-bifida, three animals, anomalies of the	
not to exceed 70% other than during		aortic arch, two animals, sternebral fusions, three animals, hyperextension of limb or	
room cleaning)		paw, one animal)	
in. The choice of vehicle was not justified in study report			
justified in study report		NOAEL maternal toxicity: 22.5 mg/kg	
GLP: Yes		bw/day NOAEL developmental toxicity: 7.5 mg/kg	
		bw/day	
Teratology range finding study	ACN (Quinoclamine)	Maternal effects:	RAR Vol. 3,
	D : 00.10/	<u>8 mg/kg bw/day:</u>	B.6.6.2.2/01
No guideline claimed in study	Purity: 98.1%	No treatment-related effects	Anonymous
Rabbit	0, 8, 20, 50, 80/8 <sup>a</sup> .	20 mg/kg bw/day:	28 (1986)
New Zealand White	200/20 <sup>a</sup> , 500/50 <sup>a</sup>	$\uparrow$ <b>post-implantation loss</b> (31.1 compared to	× ,
_		8.7 in control)	Report No:
F	Vehicle: 0.25% gum		AKJ/1/86
5/group	tragacantin	50 mg/kg bw/day:	New data for
	Gestation Days 6-18	-clinical signs (coloured urine)	the Annex I
GLP: Yes		↓ bw (Day 10: 4%, Day 14: 5%)	renewal: No
		↓ FC (Days 6-10: 49%, Days 10-14: 38%)	
		↑ <b>post-implantation loss</b> (61.0 compared to	
		8.7 in control)	
		20/9 m = /L = h = //	
		<u>80/8 mg/kg bw/day:</u>	
		Uw (Day 7. 4%, Day 8. 5%, Day 10. 4%)	
		$\downarrow$ FC (n.s.)	
		$\uparrow$ <b>post-implantation loss</b> (25.0 compared to	
		8.7 in control)	
		200/20 mg/kg hw/dav	
		-clinical signs (coloured urine)	
	r		r
--	----------------------	--	--
		↓ bw (Day 7: 6%, Day 10: 6%)	
		↓ FC (Days 6-10: 36%)	
		↑ <b>post-implantation loss</b> (30.0 compared to 8.7 in control)	
		<ul> <li>500/50 mg/kg bw/day:</li> <li>-mortality (both animals died, one died on day 9 and the other on day 10 of pregnancy)<sup>b</sup></li> <li>-clinical signs (lethargy, hunched posture, dark coloured urine)</li> <li>↓ bw (Day 8: 12%)</li> <li>↓ FC (Days 6-10: 80%)</li> </ul>	
		<u>Developmental effects:</u> <u>8 mg/kg bw/day:</u> No treatment related effects	
		20 mg/kg bw/day: ↑ post-implantation loss (31.1 compared to 8.7 in control) -malformations (spina bifida, two animals, interrupted aortic arch major, one animal, hindlimb left malrotated, one animal)	
		50 mg/kg bw/day: ↑ post-implantation loss (61.0 compared to 8.7 in control) -malformations (interrupted aortic arch major, one animal, kidney left agenesis, one animal)	
		80 mg/kg bw/day: ↑ <b>post-implantation loss</b> (25.0 compared to 8.7 in control)	
		200/20 mg/kg bw/day: ↑ post-implantation loss (30.0 compared to 8.7 in control)	
		The study is acceptable as a range finding study only. Due to low number of animals used in the study it is not considered appropriate to establish a NOAEL/LOAEL.	
Teratology study	Quinoclamine	<u>Maternal effects:</u> 5 mg/kg bw/day:	RAR Vol. 3, B.6.6.2 2/04
OECD 414	Purity: 99.0%	No treatment related effects	
Rabbit	0, 5, 17.5, 30 mg/kg		Anonymous 29 (2002)
Crl.NZW/Kbl BR	bw/day	17.5 mg/kg bw/day	Report No.:
F	Vehicle: 1% aqueous	of control)	619/155- D6154
		$\downarrow$ mean litter size (8.4 foetuses per female	D0134
24/group	Gestation Days 7-28	compared to 9.5 in control)	New data for the Annex I renewal: No
The study follows OECD TG 414 except for following deviations:		<u>30 mg/kg bw/day:</u>	

RMS: SE Co-RMS: DE

<i>i. Dosing of animals started on Day</i> 7 of gestation (the guideline	-mortality (one female killed on Day gestationc)	18 of
recommends administration to start	↓ bw (Days 4-29: 7%)	
on Day 6 of gestation) ii. During the course of study	$\downarrow$ <b>bw change</b> (Days 12-15: 0 kg com	pared to
relative humidity was within the	0.12 kg in control, Days 4-29: 46% of	
range 30-80% (the guideline	control)	
recommends the relative humidity	↓ FC (Days 7-28: 2.4%, Days 28-29:	4%)
not to exceed 70% other than during room cleaning)	<b>post-implantation loss</b> (%/No. of a	uffected
iii. The choice of vehicle was not	dams: 24.9/13 compared to 4.8/10 in a	control)
justified in study report	$\uparrow$ early intrauterine deaths (1.0 con	pared
CI Di Vac	to 0.2 in control)	1
OLP: Tes	1 <b>late intrauterine deaths</b> (1.4 comp	ared to
	0.3 in control)	
	$\downarrow$ mean litter size (7.8 foetuses per fe	emale
	compared to 9.5 in control)	
	$\downarrow$ litter weight (24%)	
	Developmental effects:	
	<u>5 mg/kg bw/day:</u>	
	No treatment related effects	
	<u>17.5 mg/kg bw/day:</u>	
	$\downarrow$ mean litter size (8.4 foetuses per fe	emale
	compared to 9.5 in control)	
	-malformations (hydronephrosis, one	;
	animal, increased incidence of abnorm	ial
	5.6% compared to 2.3% in control)	Aus.
	30 mg/kg hw/day.	
	$\uparrow$ nest implantation loss (%/No. of	offected
	dams: 24.9/13 compared to 4.8/10 in d	control)
	$\uparrow$ early intrautering deaths (1.0 con	nared
	to 0.2 in control)	ipared
	$\uparrow$ late intrauterine deaths (1.4 comm	ared to
	0.3 in control)	
	<b>mean litter size</b> (7.8 foetuses per fe	emale
	compared to 9.5 in control)	inale
	↓ litter weight (24%)	
	cnosific fostal variations (kidney)	
	avitation additional liver lobe cervit	ral
	remnant of thymus, lengthened anterio	)r
	fontanelle, incomplete ossification of	frontal
	and maxilla bones, slight fusion of	
	sternebrae, asymmetric ossification of cervical vertebral central	
	- malformations (hydronephrosis, 2 a	nimals;
	increased incidence of abnormal term	nal
	caudal vertebrae, mean % foetus: 6.49	ó
	compared to 2.3% in control; misshap	en rial ctr
	data at time for study): misaligned the	racic
	vertebral arch, one foetus, increased	
	incidence of absent frontal, mean % fo	oetus:
	8.9% compared to 0.0% in control)	
-		

NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg	
bw/day	

M: males

F: females

FC: food consumption

n.s.: not statistically significant

<sup>a</sup>In the male with macroscopically large kidneys there was also a slight increase in basophilic cortical tubules, some of which had increased mitoses compared with the occasional inactive basophilic tubules sometimes seen in controls <sup>b</sup>The high dose animals were removed from the study on Day 5 due to body weight loss and poor clinical condition

Table 2.6.3.1-2. Summary ta	ble of human data on repeated d	lose toxicity STOT RE (	(specific target organ to	oxicity-repeated
exposure)				

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
No data				

Table 2.6.3.1-3. Summary table of other studies relevant for repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

	Observations	Reference
ion about		
(as		
e)		
was	Maternal effects:	RAR Vol. 3, B.6.8.2/01
l to		
e the effects	<u>5 mg/kg bw/day:</u>	Anonymous 30 (1996)
article on	-clinical signs (coloured urine)	
onic and	-macroscopical changes (reddish	Report No.: 1312-1416-001
lopment of	discolouration of treated skin)	
en		New data for the Annex I
red during	<u>100 mg/kg bw/day:</u>	renewal: No
of	-clinical signs (encrusted skin,	
nesis. Three	coloured urine)	
twenty five	-macroscopical changes (reddish	
nature and	discolouration of treated skin)	
nale Sprague		
rl:CD	600 mg/kg bw/day:	
ats (8-12	-clinical signs (encrusted skin,	
) received	coloured urine)	
nine by	<b>↓bw loss</b> (Days 6-9: -0.41 g)	
plication at	↓ <b>bw gain</b> (Days 6-16: 31%)	
s of 5, 100	↓FC	
ng/kg	-macroscopical changes (reddish	
or 10	discolouration of treated skin)	
ve days from		
5 post-	No embryotoxicity or	
clusive.	teratogenicity was noted in this	
	study	
	NOAEL maternal: 100 mg/kg	
	bw/day	
	NOAEL terratogenia offecto: 600	
	model teratogenic effects. 000	
	III E/ KE UW/ UAY	
	The study is acceptable as	
	supplementary data only. The test	
	substance was administered	
	dermally instead of orally. The	
	ion about (as e) was l to e the effects article on onic and lopment of en red during l of nesis. Three twenty five nature and nale Sprague crl:CD ats (8-12 l) received mine by plication at ls of 5, 100 ng/kg or 10 ve days from 5 <i>post</i> - aclusive.	Ion about (as e)Observationswas l toMaternal effects: $5 mg/kg bw/day:$ -clinical signs (coloured urine) -macroscopical changes (reddish discolouration of treated skin)red during l of red during l of red during l of ats (8-12 b) received plication at ls of 5, 100 r 10100 mg/kg bw/day: -clinical signs (encrusted skin, coloured urine) -macroscopical changes (reddish discolouration of treated skin)by received r1: CD ats (8-12 b) received rice is of 5, 100 r 10 $600 mg/kg bw/day:$ -clinical signs (encrusted skin, coloured urine) $\downarrow bw loss (Days 6-9: -0.41 g)$ $\downarrow bw gain (Days 6-16: 31%)$ $\downarrow FC$ -macroscopical changes (reddish discolouration of treated skin)so f 5, 100 r 10 we days from 5 post- clusive.No embryotoxicity or teratogenicity was noted in this studyNOAEL teratogenic effects: 600 mg/kg bw/dayNOAEL teratogenic effects: 600 mg/kg bw/dayNOAEL teratogenic effects: 600 mg/kg bw/dayThe study is acceptable as supplementary data only. The test substance was administered dermally instead of orally. The

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
			choice of administration route was not justified.	

# **2.6.3.1.1** Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure (short-term and long-term toxicity)

Short-term oral toxicity was tested in rats and dogs, while short-term dermal toxicity was tested in rats. No repeated dose toxicity study performed with quinoclamine in animals by the inhalation route is available. A subchronic toxicity study conducted on quinoclamine by the inhalation route is not considered necessary since quinoclamine is not a volatile substance. It could however be noted that the acute toxicity by the inhalation route is not fully investigated.

# Rat:

# 28-day oral toxicity study in the Crl:CD®(SD)IGSBR rat:

In the 28-day oral toxicity study in the CrI:CD<sup>®</sup>(SD)IGSBR rat, treatment was associated with reduced bodyweight gain noted in males at  $\geq$ 500 ppm ( $\geq$ 44 mg/kg bw/day) and in females at 500 ppm (48 mg/kg bw/day) (n.s.) and 1000 ppm (90 mg/kg bw/day) (s.s), reduced food consumption noted in males at 1000 ppm (84 mg/kg bw/day) and in females at  $\geq$ 500 ppm, changes in haematological parameters noted in both sexes at  $\geq$ 500 ppm, changes in biochemical parameters (indicating liver toxicity) noted in males at  $\geq$ 500 ppm and in females at 1000 ppm, changes in urine analysis parameters (M: red-, brown- or dark coloured urine, increases in amorphous debris, increased urine volume; F: red-, brown- or dark coloured urine, increases in amorphous debris) noted at  $\geq$ 500 ppm, reduced thymus weights noted in both sexes at 500 ppm (At 500 ppm: eosinophilic hyaline droplets in the cytoplasm of the proximal tubular epithelium; At 1000 ppm: eosinophilic hyaline droplets in the cytoplasm of the proximal tubular epithelium, minor papillitis in two males and in one of these animals basophilic cortical tubules).

Changes in haematological parameters consisted of following statistically significant changes: reduced haemoglobin noted in males at 500 (10%) and 1000 ppm (8%) and in females at 1000 ppm (13%), reduced red blood cell count noted in males at 500 (8%) and 1000 ppm (12%) and in females at 1000 ppm (13%), reduced packed cell volume noted in males at 500 ppm (9%) and in females at 1000 ppm (11%), increased reticulocytes noted in males at 500 (95%) and 1000 ppm (170%) and in females at 1000 ppm (238%), increased red cell distribution width noted in males at 500 (30%) and 1000 ppm (37%) and in females at 500 (13%) and 1000 ppm (47%), increased haemoglobin distribution width noted in males at 500 (35%) and 1000 ppm (20%) and in females at 500 (17%) and 1000 ppm (25%), increased mean platelet volume noted in males at 1000 ppm (15%), increased platelet distribution width noted in males at 1000 ppm (24%), increased prothrombin time noted in males at

500 (60%) and 1000 ppm (85%), increased activated partial thromboplastin time noted in males at 1000 ppm (36%), increased plateletcrit noted in males at 500 ppm (38%) and in females at 1000 ppm (32%), and increased platelet noted in females at 1000 ppm (34%).

The decreased haemoglobin (up to 13%), red coloured urine (which might indicate presence of haemoglobin in the urine), presence of amorphous debris in urine, might indicate that quinoclamine causes haemolytic anaemia at high dose levels.

The NOAEL for both sexes was set at 50 ppm (equivalent to 4.7 and 5.3 mg/kg bw/day in males and females, respectively) based on reduced bodyweight noted in males at 1000 ppm and in females at  $\geq$ 500 ppm, changes in haematological parameters (indicating haemolytic anaemia) noted in both sexes at  $\geq$ 500 ppm, changes in biochemical parameters (indicating liver toxicity) noted in both sexes at 1000 ppm, changes in urine parameters noted in both sexes at  $\geq$ 500 ppm, reduced thymus weight noted in both sexes at  $\geq$ 500 ppm, enlarged kidney noted in one male at 1000 ppm, and histopathological changes in the kidneys noted in males at  $\geq$ 500 ppm (RAR Vol. 3, B.6.3.1.1/01).

### 90-day oral toxicity study in the Sprague-Dawley rat:

In the 90-day oral toxicity study in the Sprague-Dawley rat, treatment was associated with reduced bodyweight gain noted in males at 200 ppm (14 mg/kg bw/day) (6%) and in females at 1000 ppm (65 mg/kg bw/day) (7%), reduced food consumption and water consumption noted in males at 1000 ppm (62 mg/kg bw/day) and in females at  $\geq$ 50 ppm ( $\geq$ 3 mg/kg bw/day), changes in biochemical parameters (reduced serum A/G ratios noted in males at  $\geq$ 50 ppm ( $\geq$ 3 mg/kg bw/day) and in females only at the lowest dose (50 ppm), increased GOT (n.s.) noted in males at 1000 ppm), changes in organ weights noted in males at 200 ppm (increased relative right kidney, increased relative left adrenal, increased relative mandibular gland) and in both sexes at 1000 ppm (males: increased absolute and relative spleen, increased absolute and relative liver, increased absolute and relative kidney, increased relative left adrenal, increased relative mandibular gland; females: increased absolute and relative spleen, increased relative liver, increased relative kidney) and histopathological changes noted in the kidneys (increased incidence of hyaline droplets in kidney cortical tubules noted in males at  $\geq 200$  ppm), liver (bile duct proliferation noted in both sexes at 1000 ppm), spleen (increased incidence of hemosiderin deposition noted in both sexes at  $\geq$ 200 ppm ( $\geq$ 62/65 mg/kg bw/day in males and females, respectively). Increase of haemosiderin in the reticuloendothelial system is usually associated with erythrocyte destruction resulting in abnormalities normally detected in haematological examinations. In this study the haematological examinations were limited. The NOAEL in males was set at 50 ppm (3 mg/kg bw/day) based on effects on the kidneys (increased organ weight, histopathological changes) noted at  $\geq$ 200 ppm ( $\geq$ 14 mg/kg bw/day), effects on the liver (reduced serum A/G, increased organ weight, histopathological changes) noted at 1000 ppm (62 mg/kg bw/day), and effects on the spleen noted at 200 ppm (histopathological changes) and 1000 ppm (increased organ weight, histopathological changes). The NOAEL in females was set at 50 ppm (3 mg/kg bw/day) based on effects on the spleen noted at 200 ppm (13 mg/kg bw/day) (histopathological changes) and 1000 ppm (65 mg/kg bw/day) (increased organ weight, histopathological changes), effects on the liver noted at 1000 ppm (histopathological changes, increased organ weight), and effects on the kidney noted at 1000 ppm (increased organ weight) (RAR Vol. 3, B.6.3.2.1/01).

### 90-day oral toxicity study in the Crl:CD(SD)IGSBR rat:

In the 90-day oral toxicity study in the CrI:CD (SD)IGSBR rat, treatment was associated with reduced bodyweight gain noted in males at 800 ppm (56.74 mg/kg bw/day) and in all treated females, reduced food consumption noted in males at 800 ppm and in females at ≥200 ppm (≥17.81 mg/kg bw/day), changes in haematological parameters noted in both sexes at ≥200 ppm (≥13.89/17.81 mg/kg bw/day in males and females, respectively), changes in biochemical parameters noted in males at  $\geq$ 50 ppm ( $\geq$ 3.61 mg/kg bw/day) (indicating liver toxicity), changes in urinalysis parameters (dark straw coloured urine) noted in both sexes at ≥200 ppm, changes in organ weights (At 800 ppm (56.74/74.81 mg/kg bw/day in males and females, respectively): increased spleen and liver weights in both sexes, increased brain weights in males; At 200 ppm: increased spleen weight in males, increased liver weight in females, reduced thymus weight in females), histopathological changes in the spleen noted in males at 800 ppm (increased incidence of congestion, increase in the extent of haemopoiesis) and in females at 200 ppm (increase in the extent of pigment) and 800 ppm (increased incidence of congestion, textent of pigment), histopathological changes in the kidneys noted in males at 200 ppm (increase in the extent of hyaline droplets) and 800 ppm (increase in the extent of hyaline droplets, focal nephropathy, papillary interstitial eosinophilia) and in females at 800 ppm (increased incidence of pigment, focal nephropathy), histopathological changes in the liver noted in both sexes at  $\geq$ 200 ppm (sinusoidal cell pigment), and changes in thymus (minor thymus atrophy) noted in both sexes at  $\geq 200$  ppm.

Changes in haematological parameters consisted of following statistically significant changes: increased haemoglobin distribution width noted in both sexes at 200 (M: 20%, F: 32%) and 800 ppm (M: 14%, F: 24%), increased reticulocytes noted in both sexes at 200 (M: 18%, F: 82%) and 800 ppm (M: 42%, F: 135%), increased absolute reticulocytes noted in both sexes at 800 ppm (M: 59%; F: 95%) and in females at 200 (38%), reduced red blood cell count noted in both sexes at 200 (M: 5%; F: 4%) and 800 ppm (M: 13%; F: 15%), reduced packed cell volume noted in both sexes at 800 ppm (M: 11%; F: 11%) and in females at 200 ppm (5%), reduced haemoglobin noted in both sexes at 800 ppm (M: 10%; F: 11%) and in females at 200 ppm (4%), increased activated partial thromboplastin time noted in males at 200 (21%) and 800 ppm (22%), increased red cell distribution width noted in both sexes at 800 ppm (M: 16%; F: 11%), increased mean cell volume noted in females at 800 ppm (5%), reduced partial thromboplastin time noted in males at 200 (21%) and 800 ppm (22%), increased red cell distribution width noted in both sexes at 800 ppm (M: 16%; F: 11%), increased mean cell volume noted in females at 800 ppm (5%), reduced platelet distribution width noted in males at 800 ppm (10%), reduced mean cell haemoglobin noted in females at 800 ppm (5%).

No NOAEL was established for females since adverse effects on bodyweight gain were noted at the lowest dose level of 50 ppm (3.61/4.56 mg/kg bw/day in males and females, respectively) (bodyweight gain reduced 17%). The NOAEL for males was set at 50 ppm (3.61 mg/kg bw/day) based on reduced bodyweight gain noted in males at 800 ppm (56.74 mg/kg bw/day), changes in haematological parameters noted in males at  $\geq$ 200 ppm ( $\geq$ 13.89 mg/kg bw/day), changes in biochemical parameters (indicating liver toxicity) noted in males at  $\geq$ 200 ppm, changes in urinalysis parameters (dark straw coloured urine) noted in males at  $\geq$ 200 ppm, increased organ weights (spleen, liver) noted in males at  $\geq$ 200 ppm, macroscopic changes in the spleen (enlarged spleen) noted in males at 800 ppm, and histopathological changes noted in males at 800 (spleen and thymus) and  $\geq$ 200 ppm (kidney and liver) (RAR Vol. 3, B.6.3.2.1/02).

<u>28-day dermal toxicity study in the Crl:CD®(SD)IGSBR rat:</u>

In the 28-day dermal toxicity study in the Crl:CD<sup>®</sup>(SD)IGSBR rat, treatment was associated with clinical signs of skin irritation (erythema and desquamation) noted in both sexes at  $\geq 100 \text{ mg/kg bw/day}$ , changes in biochemical parameters noted in both sexes at  $\geq 300 \text{ mg/kg bw/day}$  (reduced aspartate aminotransferase and alkaline phosphatase noted in females and increased total bilirubin and glucose noted in males), dark coloured urine noted in both sexes at 1000 mg/kg bw/day, macroscopic changes (sores at the treated site) noted in females at  $\geq 100 \text{ mg/kg bw/day}$  and in males at 1000 mg/kg bw/day, and histopathological changes in the skin and kidney noted in both sexes at 1000 mg/kg bw/day. The histopathological changes in the skin consisted of increased incidence of epidermatitis noted in both sexes at 1000 mg/kg bw/day, while the histopathological changes in the kidney consisted of tubular degeneration/regeneration in the kidney cortex noted in one high dose female and in one high dose male, and hydronephrosis and pigment noted in one female.

NOAEL for systemic effects was set at 300 mg/kg bw/day based on histopathological changes in the kidneys noted in both sexes at 1000 mg/kg bw/day. No NOAEL was set for local effects due to skin irritation noted in all treated groups (RAR Vol. 3, B.6.3.4.1/01).

### 2-year combined chronic toxicity and carcinogenicity study in the rat:

In the 2-year feeding study in the Crl:CD(SD)BR rat, treatment was associated with clinical signs (orange fur staining and reduced incidence of mass bearing) noted in both sexes at 676 ppm (37.6 and 38.3 mg/kg bw/day in males and females, respectively), reduced bodyweight gain noted in females at 676 ppm (carcinogenicity evaluation: 27%; toxicology evaluation: 28%), reduced food consumption noted in both sexes at 676 ppm, changes in haematological parameters (reduced packed blood cell volume, haemoglobin concentration and red blood cell count) noted in both sexes at 676 ppm, changes in biochemical parameters noted at 676 ppm (elevated blood urea nitrogen levels noted in males (n.s) and females (n.s), reduced calcium noted in males (s.s.) and females (n.s.), reduced inorganic phosphorous noted in males (n.s.) and females (s.s.), reduced lactate dehydrogenase noted in both sexes), findings in urinalysis such as yellow/brown or orange discoloration noted in both sexes in all treated groups and diuretic males noted at 676 ppm, changes in organ weights (increased relative kidney weights noted in males at  $\geq$ 52 ppm ( $\geq$ 2.82 mg/kg bw/day), and in females at 676 ppm; increased relative spleen weights noted in females at 676 ppm; increased relative thymus weight noted in females at 676 ppm; increased relative thyroid weight noted in females at 676 ppm; increased relative heart weight noted in females at 676 ppm; increased relative adrenal weights noted in females at 676 ppm, increased relative brain weights noted in females at 676 ppm), gross pathology findings in the urinary bladder (orange discoloration) and skin (orange staining) noted in both sexes at 676 ppm, and histopathological changes noted in the urinary bladder (both sexes, ≥52 ppm corresponding to 2.82 and 3.65 mg/kg bw/day in males and females, respectively), kidneys (both sexes at  $\geq$ 52 ppm), ureter (both sexes at 676 ppm), urethra (both sexes at 676 ppm), adrenals (both sexes at 676 ppm), pancreas (both sexes at 676 ppm), parathyroid (males at 676 ppm), mammary gland (females at 676 ppm) and lungs (males at  $\geq$ 52 ppm and females at 676 ppm).

Neoplastic changes were noted in the <u>urinary bladder</u> (benign transitional cell papilloma noted in males at  $\geq$ 52 ppm and in females at 676 ppm) and <u>adrenals</u> (increased incidence of benign phaeochromocytoma noted in both sexes at 676 ppm). The benign transitional cell papilloma noted in one single male at 52 ppm was considered

of no clear relevance. No other differences in tumour incidence or type were seen which were considered to be dependent on the dose levels of ACN-technical.

Non-neoplastic changes in the <u>urinary bladder</u> consisted of: epithelial hyperplasia (both sexes at  $\geq$ 52 ppm, corresponding to  $\geq$ 2.82 and  $\geq$ 3.65 mg/kg bw/day in males and females, respectively), polyp noted in one female at 676 ppm (38.3 mg/kg bw/day) and chronic inflammation noted in both sexes at 676 ppm (37.6 and 38.3 mg/kg bw/day in males and females, respectively). Non-neoplastic changes in the <u>kidneys</u> consisted of: epithelial hyperplasia (both sexes at  $\geq$ 52 ppm), renal papillary degeneration/necrosis (both sexes at 676 ppm), increased incidence of renal cortical scarring (both sexes at 676 ppm), pelvis polyp noted in one male at 676 ppm and increased incidence of renal focal calcification (in females at  $\geq$ 52 ppm), and in the <u>parathyroid</u> (males at 676 ppm). Non-neoplastic changes in pancreas consisted of increased incidence of pancreatic acinar atrophy (both sexes at 676 ppm). The histopathological changes in the <u>mammary gland</u> consisted of decreased incidence of mammary acinar development and secretion (females at 676 ppm). Increased incidence of arterial calcification mammary at  $\geq$ 52 ppm, females at 676 ppm).

# Group 1-4 (carcinogenicity groups):

Non-neoplastic changes:

The following non-neoplastic changes were considered to be related to the dietary administration of ACN-technical:

-Hyperplasia of the urinary epithelium in the urinary bladder, kidneys and ureters at the 676 ppm and 52 ppm dose levels, and in the urethra at the 676 ppm dose level only in both males and females

	Males				Females			
	0	4	52	676	0	4	52	676
Total: number examined	50	49	47	47	49	48	49	50
Epithelial hyperplasia	3	2	5	41	1	1	6	46
Squamous metaplasia	0	0	0	0	0	0	0	3
Polyp	0	0	0	0	0	0	0	1
Cystitis/inflammation	1	2	1	3	0	0	0	2
Haemorrhage	0	0	0	1	0	0	0	2
Terminal kill: number examined	27	27	20	30	26	29	30	38
Epithelial hyperplasia	0	0	0	28	1	1	0	35
Squamous metaplasia	0	0	0	0	0	0	0	2
Polyp	0	0	0	0	0	0	0	1
Cystitis/inflammation	0	0	0	0	0	0	0	2
Haemorrhage	0	0	0	0	0	0	0	2
Killed in extremis: number examined	17	18	21	6	19	16	19	10
Epithelial hyperplasia	2	2	4	5	0	0	6	9
Squamous metaplasia	0	0	0	0	0	0	0	1
Polyp	0	0	0	0	0	0	0	0
Cystitis/inflammation	0	2	0	1	0	0	0	0
Haemorrhage	0	0	0	0	0	0	0	0
Died: number examined	6	4	6	11	4	3	0	2
Epithelial hyperplasia	1	0	1	8	0	0	0	2
Squamous metaplasia	0	0	0	0	0	0	0	0
Polyp	0	0	0	0	0	0	0	0

# Non-neoplastic pathology-urinary bladder (groups 1-4)

RMS: SE Co-RMS: DE

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Cystitis/inflammation	1	0	1	2	0	0	0	0
Haemorrhage	0	0	0	1	0	0	0	0

# Non-neoplastic pathology-kidneys (groups 1-4)

	Males				Females				
	0	4	52	676	0	4	52	676	
Total: number examined	50	49	48	48	50	50	50	50	
Epithelial hyperplasia	2	5	12	39	2	0	10	34	
Papillary necrosis	0	1	0	9	0	0	0	3	
Papillary focal necrosis	0	2	1	12	0	0	0	0	
Papilla haemorrhage/haemorrhage	2	0	1	10	0	5	1	6	
Paiplla focal calcification	0	0	0	3	0	0	0	0	
Cortical scar	3	3	2	11	0	0	1	6	
Focal calcification	3	2	6	5	24	24	32	36	
Terminal kill: number examined	27	27	20	30	26	29	30	38	
Epithelial hyperplasia	1	4	6	25	0	0	3	29	
Papillary necrosis	0	1	0	6	0	0	0	2	
Papillary focal necrosis	0	2	0	10	0	0	0	0	
Papilla haemorrhage/haemorrhage	0	0	1	9	0	4	1	6	
Papilla focal calcification	0	0	0	3	0	0	0	0	
Cortical scar	3	3	1	8	0	0	0	5	
Focal calcification	1	1	4	2	16	13	21	30	
Killed in extremis: number examined	17	18	21	6	19	16	19	10	
Epithelial hyperplasia	1	1	4	6	1	0	7	4	
Papillary necrosis	0	0	0	1	0	0	0	1	
Papillary focal necrosis	0	0	1	1	0	0	0	0	
Papilla haemorrhage/haemorrhage	1	0	0	0	0	0	0	0	
Papilla focal calcification	0	0	0	0	0	0	0	0	
Cortical scar	0	0	1	1	0	0	1	1	
Focal calcification	2	1	1	2	5	8	10	4	
Died: Number examined	6	4	7	12	5	5	1	2	
Epithelial hyperplasia	0	0	2	8	1	0	0	1	
Papillary necrosis	0	0	0	2	0	0	0	0	
Papillary focal necrosis	0	0	0	1	0	0	0	0	
Cortical scar	0	0	0	2	0	0	0	0	
Focal calcification	0	0	1	1	3	3	1	2	

# Non-neoplastic pathology-ureters and urethra (groups 1-4)

	Males				Females			
	0	4	52	676	0	4	52	676
Ureters								
Total: number examined	47	21	26	38	48	20	21	47
Epithelial hyperplasia	0	1	2	19	0	0	5	21
Haemorrhage	0	0	0	1	0	0	0	1
Metaplasia/keratin	0	0	0	0	0	0	0	1
Terminal kill: number examined	26	3	0	26	26	1	2	35
Epithelial hyperplasia	0	0	0	13	0	0	1	15
Haemorrhage	0	0	0	0	0	0	0	1
Metaplasia/keratin	0	0	0	0	0	0	0	1
Killed in extremis: number examined	16	15	21	6	18	15	18	10
Epithelial hyperplasia	0	1	1	3	0	0	4	5
Haemmorrhage	0	0	0	0	0	0	0	0
Metaplasia/keratin	0	0	0	0	0	0	0	0
Died: Number examined	5	3	5	6	4	4	1	2
Epithelial hyperplasia	0	0	1	3	0	0	0	1
Hamorrhage	0	0	0	1	0	0	0	0
Metaplasia/keratin	0	0	0	0	0	0	0	0
Urethra								
Total: number examined	44	33	35	41	42	18	13	36
Epithelial hyperplasia	1	0	0	4	1	1	0	6
Terminal kill: number examined	23	16	11	27	21	0	1	27
Epithelial hyperplasia	0	0	0	1	1	0	0	2

Killed in extremis: number examined	15	13	18	6	16	13	11	7
Epithelial hyperplasia	1	0	0	3	0	1	0	4
Died: number examined	6	4	6	8	5	5	1	2
Epithelial hyperplasia	0	0	0	0	0	0	0	0

The polyp seen in the urinary bladder of one high dose terminal kill female probably developed as a response to the irritant toxic effect of the test compound on the urothelium, according to study author.

-Renal papillary necrosis and an increased incidence of renal cortical scarring in the kidneys at the 676 ppm dose level only in males and females. The severity of the papillary necrosis which was often accompanied by haemorrhage in this carcinogenicity study was greater than that seen at any stage of the toxicity study and this lesion was considered to have been the cause of death or predominant pathology in six terminal kill and three decedent high dose animals.

-An increased incidence and severity of pancreatic acinar atrophy at the 676 ppm dose level in males and females

	Males				Females			
	0	4	52	676	0	4	52	676
Total: number examined	50	28	29	46	48	20	23	50
Acinar atrophy- minimal	14	12	12	15	10	3	8	19
Acinar atrophy-moderate	3	1	4	14	0	0	0	9
Acinar atrophy- marked	0	0	1	5	0	0	1	7
Acinar atrophy- total	17	13	17	34	10	3	9	35
Fatty infiltration	11	6	3	14	6	1	3	10
Chronic inflammation	3	0	0	2	2	1	2	7
Terminal kill: number examined	27	6	1	30	25	1	3	38
Acinar atrophy- minimal	10	0	0	9	4	0	2	15
Acinar atrophy- moderate	1	0	0	11	0	0	0	6
Acinar atrophy- marked	0	0	0	5	0	0	0	7
Acinar atrophy-total	11	0	0	25	4	0	2	28
Fatty infiltration	5	0	0	10	3	0	1	8
Chronic inflammation	2	0	0	0	0	0	0	5
Killed in extremis: number examined	17	18	21	6	19	16	19	10
Acinar atrophy- minimal	3	12	11	2	4	3	6	3
Acinar atrophy- moderate	1	1	4	2	0	0	0	2
Acinar atrophy- marked	0	0	0	0	0	0	1	0
Acinar atrophy- total	4	13	15	4	4	3	7	5
Fatty infiltration	5	6	3	3	3	1	2	2
Chronic inflammation	0	0	0	0	2	1	2	2
Died: number examined	6	4	7	10	4	3	1	2
Acinar atrophy- minimal	1	0	1	4	2	0	0	1
Acinar atrophy – moderate	1	0	0	1	0	0	0	1
Acinar atrophy- marked	0	0	1	0	0	0	0	0
Acinar atrophy- total	2	0	2	5	2	0	0	2
Fatty infiltration	1	0	0	1	0	0	0	0
Chronic inflammation	1	0	0	2	0	0	0	0

Non-neoplastic pathology- pancreas (groups 1-4)

-A decrease in the incidence of mammary acinar development and secretion in 676 ppm females only. This effect was probably related to the reduced food consumption and the lower bodyweight in these high dose animals, according to the study author.

	Females			
	0	4	52	676
Mammary gland (cranial)				
Total: number examined	50	22	22	50
Acinar development	25	13	12	15
Secretion	15	7	7	7
Terminal kill: number examined	26	1	2	38
Acinar development	13	0	1	12
Secretion	8	0	0	4
Killed in extremis: number examined	19	16	19	10
Acinar development	8	8	10	2
Secretion	6	3	6	2
Died: number examined	5	5	1	2
Acinar development	4	5	1	1
Secretion	1	4	1	1
Mammary gland (caudal)				
Total: number examined	50	23	22	50
Acinar development	32	16	18	28
Secretion	21	11	13	15
Terminal kill: number examined	26	2	2	38
Acinar development	18	0	2	22
Secretion	11	0	2	10
Killed in extremis: number examined	19	16	19	10
Acinar development	9	11	16	5
Secretion	7	6	11	4
Died: number examined	5	5	1	2
Acinar development	5	5	0	1
Secretion	3	5	0	1

Non-neoplastic pathology- Mammary gland (groups 1-4 females)

-A decrease in the incidence of skin and tail scab formation in 676 ppm males, only. These effects might be related to reduced food consumption and lower body weight gain according to the study author.

Non-neoplastic pathology-skin and tail lesions (groups 1-4)

	Males				Females			
	0	4	52	676	0	4	52	676
Total: number examined	50	50	50	50	50	50	50	50
Scab formation (all sites)	18	21	17	6	5	8	6	3
Tail abcesses	21	17	15	7	10	6	6	1
Terminal kill: examined	27	27	20	30	26	29	30	38
Scab formation (all sites)	7	15	7	5	3	6	1	2
Tail abcesses	11	9	4	4	8	3	2	1
Killed in extremis: number examined	17	18	21	6	19	16	19	10
Scab formation (all sites)	9	5	10	0	2	1	4	1
Tail abcessesAcinar atrophy- minimal	9	6	9	2	1	3	4	0
Died: number examined	6	5	9	14	5	5	1	2
Scab formation (all sites9	2	1	0	1	0	1	1	0
Tail abcesses	1	2	2	1	1	0	0	0

-A decrease in the incidence of tail abscess formation in 676 ppm males and females. This effect might be related to reduced food consumption and lower body weight gain according to the study author.

-A small increase in the incidence of arterial calcification in the lungs of males and females from the 676 ppm group and males from the 52 ppm dose group, and renal focal calcification in females from the 676 ppm and

52 ppm dose groups. According to study author it is possible that these effects together with a related small increase in the incidence of parathyroid hyperplasia in terminal kill and decedent high dose males were indicative of alterations in blood calcium levels due to interference in the renal regulation of phosphorus and calcium ions. It is possible that the treatment-related kidney lesions could have affected these excretory mechanism.

Non-neoplastic pathology- lungs (groups 1-4)

	Males				Females			
	0	4	52	676	0	4	52	676
Total: number examined	50	50	49	48	50	50	50	50
Arterial calcification	6	7	16	18	7	8	9	12
Terminal kill: number examined	27	27	20	30	26	29	30	38
Arterial calcification	1	2	7	10	0	5	4	9
Killed in extremis: number examined	17	18	21	6	19	16	19	10
Arterial calcification	3	4	8	2	6	3	5	2
Died: number examined	6	5	8	12	5	5	1	2
Arterial calcification	2	1	1	6	1	0	0	1

-A small increase in the incidence of parathyroid hyperplasia in both terminal kill and decedent high dose males

	Males				Females			
	0	4	52	676	0	4	52	676
Total: number examined	42	20	22	30	45	14	20	42
Hyperplasia	0	2	0	5	0	0	0	1
Terminal kill: number examined	23	1	0	19	25	1	2	32
Hyperplasia	0	0	0	3	0	0	0	0
Killed in extremis: number examined	15	15	17	5	17	11	18	8
Hyperplasia	0	1	0	1	0	0	0	1
Died: number examined	4	4	5	6	3	2	0	2
Hyperplasia	0	1	0	1	0	0	0	0

Non-neoplastic pathology- parathyroids (groups 1-4)

# Group 5-8 (toxicology groups):

Non-neoplastic changes:

<u>Week 26 to 78 interim kill:</u> Treatment related histopathological changes were initially confined to urinary bladders of high dose (676 ppm) animals (week 26) and comprised epithelial hyperplasia and chronic inflammatory changes.

Non-neoplastic pathology Week 26 interim kill: Urinary bladder (groups 5-8)

	Males				Females				
	0	4	52	676	0	4	52	676	
Total: number examined	10	9	10	10	10	10	10	10	
Epithelial hyperplasia	0	0	1	5	0	1	2	5	
Chronic inflammation	0	1	0	4	0	1	0	0	
Cystitis with focal hyperplasia	0	0	0	0	1	0	0	0	
Eosinophilic plug	0	2	2	1	0	0	0	0	

As the study progressed similar lesions appeared in occasional intermediate dose animals and were more widespread, affecting the ureters (epithelial hyperplasia seen in 3/7 high dose males and 4/8 females), urethras (epithelial hyperplasia seen in 1/6 high dose males) and kidneys as well as urinary bladders at the week 78 interim

kill. At week 52 cortical scars in the kidneys were seen in two out of ten high dose males. Changes seen in the kidneys noted at 78 interim kill showed a clear treatment and dose-related incidence included minimal and focal hyperplasia of the renal papillary and pelvic epithelium, minimal degeneration or necrosis in the papillae, a necrosis was confined to the tip of the papilla. The polyp present in the renal pelvis of a high dose male consisted of fibro-fatty tissue covered by hyperplastic epithelium. The hyperplasia of the pelvic epithelium seen in one control male was associated with the presence of calculi (stones).

# Terminal (104 week) kill:

<u>Urinary bladder:</u> Epithelial hyperplasia was seen only in treated animals and was characterised by a generalised increase in the number of layers of cells in the urinary epithelium. The normal epithelium consisted of two to three layers of cells, minimal hyperplasia by five to eight layers of cells and marked hyperplasia by more than eight layers of cells. In several animals two degrees of hyperplasia were seen with focal area of moderate hyperplasia associated with diffuse minimal hyperplasia. Squamous metaplasia of the urinary epithelium was associated with epithelial hyperplasia in two high dose females. Epithelial haemorrhage was noted in two male and one female high dose animals. Acute inflammation was seen in association with a bladder tumour in an intermediate dose male.

Non-neoplastic pathology Terminal (104 week) kill: Urinary bladder (groups 5-8)

	Males				Females				
	0	4	52	676	0	4	52	676	
Total: number examined	9	10	9	5	11	9	10	15	
Epithelial hyperplasia- total	0	0	2	5	1	0	0	15	
Squamous metaplasia	0	0	0	0	0	0	0	2	
Haemorrhage	0	0	0	2	0	0	0	1	
Cystitis/acute inflammation	0	0	1	0	0	0	0	0	
Chronic inflammation	0	0	1	0	1	0	1	0	
Eosinophilic plug	0	0	1	0	0	0	0	0	

Kidneys: Varying degrees of simple epithelial hyperplasia involving the renal pelvis and papilla, squamous

metaplasia of the pelvic epithelium and cortical scars showed a treatment related increase in high dose animals

Non-neoplastic pathology Terminal (104 week) kill: Kidneys (groups 5-8)

	Males				Females				
	0	4	52	676	0	4	52	676	
Number examined	9	10	9	5	11	9	10	15	
Epithelial hyperplasia- papilla/pelvis	1	0	4	4	0	0	1	8	
Squamous metaplasia	0	0	0	0	0	0	0	1	
Papillary degeneration/necrosis	0	1	0	0	0	0	0	0	
Cortical scars	1	1	2	1	0	1	0	3	

<u>Ureters:</u> A clear increase in the incidence of epithelial hyperplasia was seen in high dose group animals. Squamous metaplasia was seen in one high dose female. Acute inflammation and haemorrhage were seen in two separate high dose females

Non-neoplastic pathology Terminal (104 week) kill: Ureters (groups 5-8)

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	0	4	52	676	0	4	52	676
Number examined	7	10	8	5	11	8	9	11
Epithelial hyperplasia	0	0	1	3	1	0	1	5
Squamous metaplasia	0	0	0	0	0	0	0	1
Acute inflammation	0	0	0	0	0	0	0	1
Haemorrhage	0	0	0	0	0	0	0	1

Urethra: There was an increased incidence of epithelial hyperplasia in high dose females

Non-neoplastic pathology Terminal (104 week) kill: Urethra (groups 5-8)

	Males				Females			
	0	4	52	676	0	4	52	676
Number examined	7	10	9	4	8	7	9	11
Epithelial hyperplasia	0	0	1	0	1	1	0	3

<u>Pancreas:</u> Varying degrees of acinar atrophy were seen in a proportion of animals from both control and treatment groups. Both the incidence and severity of this change were increased in both sexes of the high dose group compared with the controls

Non-neoplastic pathology Terminal (104 week) kill: Pancreas (groups 5-8)

	Males				Females			
	0	4	52	676	0	4	52	676
Killed in extremis-Number examined	9	10	12	11	7	8	7	3
Acinar atrophy-minimal	1	1	2	4	0	1	3	1
Acinar atrophy-moderate	1	1	2	2	0	0	0	1
Acinar atrophy-marked	0	0	0	1	0	0	0	0
Acinar atrophy-total	2	2	4	7	0	1	3	2
Died: number examined	3	3	5	7	4	3	4	2
Acinar atrophy-minimal	0	0	1	3	0	0	0	1
Acinar atrophy-moderate	0	0	0	0	0	0	0	0
Acinar atrophy-marked	0	0	0	0	0	0	0	0
Total	0	0	1	3	0	0	0	1

<u>Mammary Glands</u>: Varying degrees of acinar development and secretion were seen in the mammary tissue of a proportion of females from both control and treatment groups. There was a decrease in the incidence of these changes in high dose animals compared with controls which was most clearly seen in the cranial mammary gland

Non-neoplastic pathology Terminal (104 week) kill: Mammary Glands (groups 5-8)

	Females			
	0	4	52	676
Caudal mammary gland				
Number examined	11	8	10	15
Acinar development	7	6	7	7
Secretion	3	6	3	0
Cranial mammary gland				
Number examined	11	8	10	15
Acinar development	8	4	4	2
Secretion	5	4	3	1

NOAEL for systemic toxicity was 4 ppm (corresponding to 0.21 and 0.28 mg/kg bw/day for males and females, respectively) based on reduced bodyweight gain noted in females at 676 ppm (38.3 mg/kg bw/day), changes in

haematological parameters noted in both sexes at 676 ppm (37.6 and 38.3 mg/kg bw/day in males and females, respectively), changes in biochemical parameters noted in both sexes at 676 ppm, changes in organ weights (increased kidney weight noted in males at  $\geq$ 52 ppm and in females at 676 ppm; increased thyroid, thymus, heart and adrenals noted in females at 676 ppm), changes in urinalysis noted in both sexes at  $\geq$ 52 ppm (At 52 ppm and 676 ppm: yellow/brown to orange discoloration; At 676 ppm: diuretic males), macroscopic changes noted in both sexes at  $\geq$ 52 ppm.

NOAEL for tumour incidence was 52 ppm (corresponding to 2.82 and 3.65 mg/kg bw/day in males and females, respectively) based on benign transitional cell papillomas in urinary bladder and increased incidence of benign phaeochromocytoma in adrenals noted in both sexes at 676 ppm (RAR Vol. 3, B.6.5.1/01)

### Two generation reproductive toxicity study:

The study is no GLP study and considered limited due to several deviations from the OECD TG 416. In the study, groups of 25 male and 25 female Sprague-Dawley rats received K-1616 (quinoclamine) in the diet at dose level up to 500 ppm (corresponding to 30.9 and 37.7 mg/kg bw/day in F0 males and females, respectively, and 37.0 and 43.8 mg/kg bw/day in F1 males and females, respectively) through two successive generations. Treatment with the test substance did not affect mating performance or fertility of the male and female parental animals and no consistent differences from control values were noted in comparisons of parental food consumption, survival rates and parturition indices or postnatal and postweaning survival. In addition, evaluations of the data obtained from foetuses taken by caesarean section did not reveal any findings indication teratogenic effects of the test substance at any of these concentrations.

Differences from control group data noted at the high dose level (500 ppm) included lower growth period mean body weight values in the P1 (4% at week 13) and P2 (10% at week 9) generation males and P2 generation females (10% at week 9), reduced bodyweight gain in P1 (7%) and P2 (11%) generation males and P2 (9%) generation females, lower mean offspring weights at weaning in all filial generations (F1a: 13% and 7% in males and females, respectively; F1b: 14% and 9% in males and females, respectively; F2a: 8% and 9% in males and females, respectively; F2b: 11% and 5% in males and females, respectively), an increase in the observations of hunched appearance during the growth periods of both parental generations, and an increased incidence of gray lung cysts and orange-stained fur noted in the F2b offspring at necropsy. Mean litter size in F2a and F2b generations were also reduced at this dose level.

Differences noted to a lesser degree at the mid dose level (25 ppm) included slightly lower mean body weight values in the P1 (1% at week 13) and P2 (7% at week 9) generation males and P2 (5% at week 9) generation females at the last weighing interval of the growth periods, reduced bodyweight gain in P1 (2%) and P2 (11%) generation males and P2 (6%) generation females, an occasional slight increase in the observations of hunched appearance in both parental generations, and an increased incidence of gray lung cysts in the F2b offspring at necropsy.

Differences noted to a lesser degree at the low dose level (1 ppm) included slightly lower mean body weight values in the P1 (3%) and P2 (7%) generation males and P2 (4%) generation females at the last weighing interval of the growth periods, reduced bodyweight gain in P1 (4%) and P2 (11%) generation males and P2 (4%)

generation females, an occasional slight increase in the observations of hunched appearance in both parental generations, and an increased incidence of lung cysts in the F2b offspring at necropsy. Increased incidence of gray lung cysts was noted in the F2b offspring reared for three months (at 1 ppm: 8 compared to 11 in control group; at 25 ppm: 29 compared to 11 in control group; at 500 ppm: 39 compared to control group). The findings of gray lung cysts in the F2b offspring was dose related although the relevance of this finding is not clear. The finding was not observed in the offspring of the F1b generation reared for 5 weeks or in other available toxicological studies on quinoclamine. Thus, it seems to be a finding occurring in adult F2b animals including control animals. In the high dose group the incidence of gray cysts was 3.5 times higher when compared to controls, and therefore considered adverse. In the low and mid-dose groups the incidences were less marked (1.6 to 2.6 times higher when compared to controls) and not considered adverse in the absence of other effects in the offsprings at these dose levels.

The NOAEL for parental animals was set at 25 ppm (1.6 mg/kg bw/day) based on clinical signs (hunched posture) noted in P1 and P2 generation animals at 500 ppm (37 mg/kg bw/day), reduced body weight noted in P2 males and females at 500 ppm, and reduced bodyweight gain noted in P2 males at 500 ppm. The NOAEL for offsprings was set at 25 ppm (1.6 mg/kg bw/day) based on reduced body weights at weaning in all filial generations noted at 500 ppm (37 mg/kg bw/day) and gray lung cysts noted in P2 offspring reared for 3 months at 500 ppm. The NOAEL for reproductive toxicity was set at 500 ppm (37 mg/kg bw/day) (RAR Vol. 3. B.6.6.1/01).

### Teratology study in the rat:

Female CD rats of Sprague-Dawley origin (CD(SD)BR) were administered quinoclamine orally by gavage at doses up to 75 mg/kg bw/day. Treatment was associated with reduced bodyweight gain (25%) and food consumption noted in dams at 75 mg/kg bw/day, changes in gross pathology (enlarged spleen) noted in dams at  $\geq 20$  mg/kg bw/day, reduced foetal weight (7%) noted at 75 mg/kg bw/day and increased incidence of aortic abnormalities and skeletal variations noted at  $\geq 20$  mg/kg bw/day. The increased incidence of aortic abnormalities included innominate artery absent noted at  $\geq 20$  mg/kg bw/day and situs inversus and interrupt aortic arch noted at 75 mg/kg bw/day. The increased incidence of skeletal variants included effects on skull (hyoid not ossified) and vertebrae (thoracic centre one or more bilobed) noted at  $\geq 20$  mg/kg bw/day and effects on sternebrae (5th and 6th not ossified; one or more bilobed, bipartite or misaligned) noted at 75 mg/kg bw/day. The NOAEL for maternal toxicity was 5 mg/kg bw/day based on reduced bodyweight gain (25%) noted in dams at 75 mg/kg bw/day and changes in gross pathology (enlarged spleen) noted at  $\geq 20$  mg/kg bw/day. NOAEL for developmental toxicity was 5 mg/kg bw/day based on reduced bodyweight (7%) noted at 75 mg/kg bw/day and increased incidence of aortic abnormalities and skeletal variations noted at  $\geq 20$  mg/kg bw/day. NOAEL for developmental toxicity was 5 mg/kg bw/day based on reduced foetal weight (7%) noted at 75 mg/kg bw/day and increased incidence of aortic abnormalities and skeletal variations noted at  $\geq 20$  mg/kg bw/day (RAR Vol. 3, B.6.6.2.1/02).

# Teratology study in the rat:

Female CrI:CD(SD)IGSBR rats were administered quinoclamine orally by gavage at doses up to 75 mg/kg bw/day. Treatment was associated with maternal clinical signs noted in dams at 20 mg/kg bw/day (paddling of the forelimbs) and 75 mg/kg bw/day (paddling of the forelimbs and nose rubbing), reduced maternal bodyweight gain noted in dams at 20 mg/kg bw/day (Days 7-8: 62%, Days 17-19: 21%) and 75 mg/kg bw/day (Days 17-19: 41%),

maternal bodyweight loss noted in dams at 75 mg/kg bw/day (Days 6-7: -4.6 g, Days 7-8: -2.6 g, Days 8-9: -0.4 g), reduced food consumption noted in dams at  $\geq 20 \text{ mg/kg bw/day}$ , reduced gravid uterus weight noted at  $\geq$ 20 mg/kg bw/day, reduced number of early intrauterine deaths noted at 75 mg/kg bw/day, reduced litter weight noted at ≥20 mg/kg bw/day, increased post-implantations loss noted at 75 mg/kg bw/day, reduced mean litter size noted at 75 mg/kg bw/day, reduced foetal weight noted at 20 mg/kg bw/day (7%) and 75 mg/kg bw/day (12%), increased incidence of skeletal variations (incomplete ossification of skull bone (frontal and nasal) and unossified fifth sternebrae) noted at  $\geq 20 \text{ mg/kg bw/day}$ , and malformations noted at 75 mg/kg bw/day. The observed malformations noted at 75 mg/kg bw/day consisted of subcutaneous oedema (one animal), retro-oesophageal aortic arch (one animal), kidney misshapen (one animal), and hydropnephrosis (three animals). NOAEL for maternal toxicity was 5 mg/kg bw/day based on reduced bodyweight gain noted in dams at  $\geq 20$  mg/kg bw/day, body weight loss noted in dams at 75 mg/kg bw/day, reduced mean gravid uterus weight noted in dams at  $\geq$ 20 mg/kg bw/day, reduced mean litter weight noted at  $\geq$ 20 mg/kg bw/day, increased number of pre- and postimplantation losses and early intrauterine deaths noted at 75 mg/kg bw/day, and reduced mean litter size noted at 75 mg/kg bw/day. NOAEL for developmental toxicity was 5 mg/kg bw/day based on reduced foetal weight noted at  $\geq 20 \text{ mg/kg bw/day}$ , increased number of post-implantation loss and early intrauterine deaths noted at 75 mg/kg bw/day, reduced mean litter size noted at 75 mg/kg bw/day, increased incidence of skeletal variations noted at ≥20 mg/kg bw/day, and malformations noted at 75 mg/kg bw/day (RAR Vol. 3, B.6.6.2.1/04).

# Terotology study in the rat (dermal exposure):

In the dermal embryo-foetal development study in the rat, treatment was associated with clinical signs (coloured urine noted at  $\geq$ 5 mg/kg bw/day and encrusted skin noted at  $\geq$ 100 mg/kg bw/day), reduced bodyweight growth noted at 600 mg/kg bw/day (bodyweight loss: -0.41 g, reduced bodyweight gain Days 6-16: 31%), reduced food consumption, and macroscopical changes (reddish discolouration of treated skin). No embryotoxicity or teratogenicity was noted (RAR Vol. 3, B.6.6.2.1/04).

# Mouse:

# 80-week carcinogenicity study in the mouse:

In the 80-week carcinogenicity study in the CrI:CD-1(ICR)BR mouse, treatment was associated with clinical signs (orange fur staining) noted in both sexes at  $\geq$ 3 ppm, increased mortality noted in both sexes at  $\geq$ 30 ppm, reduced bodyweight gain (33% in males, 30% in females) noted at  $\geq$ 300 ppm, changes in organ weight noted at  $\geq$ 30 ppm (increased relative liver weight noted in females at 300 ppm, increased relative kidney weights (n.s.) noted in males at  $\geq$ 30 ppm and in females at 300 ppm, increased relative heart and brain weights noted in females at 300 ppm), histopathological changes (At 300 ppm: increased incidence of malignant lymphoma noted in females, increased incidence of adrenal spindle cell hyperplasia noted in males, increased incidence of adrenal atrophy noted in females, kidney cortical scarring and hydronephrosis noted in both sexes, hepatic chronic inflammation and brown pigmentation noted in females, sciatic nerve degeneration noted in females, spleenic haemosiderosis noted in females, generalised periarteritis in females, myocardial fibrosis in particularly in males, hyperkeratosis in the stomach noted in both sexes, epithelial hyperplasia (males) and dilation of mucosal glands of the stomach (both sexes), epithelial hyperplasia of the urinary bladder (particularly in females), dilatation of the ureters in both

sexes and histiocytosis of lymph nodes in both sexes; At 30 ppm: adrenal spindle cell hyperplasia and adrenal atrophy noted in females, and hyperkeratosis and chronic inflammation in the stomach in females).

NOAEL was 3 ppm (0.38 and 0.44 mg/kg bw/day for males and females, respectively) based on increased mortality noted in both sexes at  $\geq$ 30 ppm, reduced bodyweight gain (33% in males, 30% in females) noted at  $\geq$ 300 ppm, increased relative liver weight noted in females at 300 ppm, increased relative kidney weights noted in males at  $\geq$ 30 ppm and in females at 300 ppm and histopathological changes noted in the adrenal and stomach at  $\geq$ 30 ppm and in the kidney, urether, urinary bladder, liver, sciatic nerve, spleen, heart and lymph nodes noted at 300 ppm, and increased incidence of malignant lymphoma noted in females at 300 ppm (RAR Vol. 3, B.6.5.2/01)

### Dog:

# 28-day oral toxicity study in the dog:

In the 28-day oral toxicity study in the Beagle dog, treatment was associated with clinical signs of coloured urine noted in females at  $\geq 10 \text{ mg/kg bw/day}$  and in males at  $\geq 30 \text{ mg/kg bw/day}$ . At 100 mg/kg bw/day subdued behaviour (F) and vomiting (M, F) were noted in addition. Body weights and food consumption were reduced in these high dosed animals (on Day 4 the reduction in body weights were 13% in the male and 18% in the female). Due to body weight loss and poor clinical condition high dosed (100 mg/kg bw/day) animals were removed from study on Day 5. Changes in clinical chemistry were also noted in the high dosed animals (reduced plasma sodium, potassium and chloride concentrations, increased plasma urea, total bilirubin, creatinine and total cholesterol concentrations). Changes in organ weights were noted in both sexes at ≥30 mg/kg bw/day (At 30 mg/kg bw/day: increased spleen; At 100 mg/kg bw/day: increased spleen, kidney and liver). Macroscopic changes in the urinary bladder (abnormal urinary bladder contents) was noted in the high dosed female (100 mg/kg bw/day), and histopathological changes in the kidney and urinary bladder were noted in both sexes at  $\geq$  30 mg/kg bw/day. Histopathological changes in the kidney consisted of tubular nephropathy and transitional cell hyperplasia (both sexes at  $\geq$  30 mg/kg bw/day), while the histopathological changes in the urinary bladder consisted of transitional cell hyperplasia (both sexes at  $\geq$ 30 mg/kg bw/day), arteritis (both sexes at 100 mg/kg bw/day) and epithelial necrosis (male at 100 mg/kg bw/day). The study was acceptable as a range finding study but not for NOAEL/LOAEL setting (RAR Vol. 3, B.6.3.1.2/01).

# 90-day oral toxicity study in the dog:

In the 90-day oral toxicity study in the Beagle dog, treatment was associated with clinical signs (coloured urine and faeces) noted in both sexes at  $\geq 3 \text{ mg/kg}$  bw/day, reduced bodyweight gain noted in females at  $\geq 10 \text{ mg/kg}$ bw/day (12% n.s.) and in both sexes at 30 mg/kg bw/day (males: 31%; females: 35%), reduced food consumption noted in males at  $\geq 10 \text{ mg/kg}$  bw/day and in females at 30 mg/kg bw/day, changes in haematological parameters noted in both sexes at  $\geq 10 \text{ mg/kg}$  bw/day, changes in biochemical parameters (increased mean total bilirubin) noted in both sexes at 30 mg/kg bw/day, changes in organ weights (increased adjusted liver weight noted in females at  $\geq 10 \text{ mg/kg}$  bw/day and in males at 30 mg/kg bw/day, increased adjusted thyroid/parathyroid noted in males at  $\geq 10 \text{ mg/kg}$  bw/day, increased adjusted spleen weight noted in females at 30 mg/kg bw/day), gross pathology changes (enlarged spleen noted in two females at 30 mg/kg bw/day, mottled liver noted in one female at 30 mg/kg bw/day, red urinary bladder noted in one female at 30 mg/kg bw/day), histopathological changes in bone marrow (both sexes at  $\geq 10$  mg/kg bw/day), liver (both sexes at  $\geq 10$  mg/kg bw/day), urinary bladder (in females at  $\geq 10$  mg/kg bw/day, in males at 30 mg/kg bw/day), spleen (in both sexes at 30 mg/kg bw/day), kidney (in both sexes at 30 mg/kg bw/day).

The haematological changes consisted of following changes: reduced red blood cell count noted in both sexes at 10 (M: 10%; F: 9%) and 30 mg/kg bw/day (19%), reduced haemoglobin noted in both sexes at 30 mg/kg bw/day (M: 18%; F: 19%), reduced mean cell volume noted in both sexes at 30 mg/kg bw/day (14%), increased reticulocytes noted in both sexes at 10 (M: 100%; F: 83%) and 30 mg/kg bw/day (M: 187%; F: 175%), increased Ret/ABS noted in both sexes at 30 mg/kg bw/day (M: 118%; F: 125%) and in males at 10 mg/kg bw/day (73%), reduced mean cell haemoglobin concentration noted in both sexes at 10 mg/kg bw/day (M: 3%; F: 2%) and 30 mg/kg bw/day (M: 50%; F: 54%), increased total white blood cell noted in both sexes at 30 mg/kg bw/day (M: 38%; F: 27%).

The histopathological changes consisted of findings in haemopoietic tissues and in the liver and urinary system. There was increased haemopoiesis in the bone marrow and spleen together with the increase in iron-containing pigment in the liver, this was indicative for low grade haemolytic anaemia and correlated with the findings of reduced red blood cell count and haemoglobin concentration and increased reticulocyte count observed in the intermediate and high dose groups. The increased white blood cell count may be related to the general increase in haemopoiesis noted in the bone marrow. In the kidney pigment, characterised by yellow-brown cytoplasmic droplets, was seen. In addition, some high dose animals had bile duct hyperplasia in the liver and transitional cell hyperplasia in the urinary bladder. One high dose animal also had minor arteritis in the urinary bladder and one had cystitis.

NOAEL for both sexes was set at 3 mg/kg bw/day based on reduced bodyweight gain noted in females at  $\geq 10$  mg/kg bw/day and in males at 30 mg/kg bw/day, changes in haematological parameters (indicating haemolytic anaemia) noted in both sexes at  $\geq 10$  mg/kg bw/day, changes in biochemical parameters (indicating liver toxicity) noted in both sexes at 30 mg/kg bw/day, increased liver weight (noted in females at  $\geq 10$  mg/kg bw/day and in males at 30 mg/kg bw/day), increased thyroid/parathyroid weight noted in males at  $\geq 10$  mg/kg bw/day, increased spleen weight noted in females at 30 mg/kg bw/day), gross pathology changes noted in females at 30 mg/kg bw/day (enlarged spleen, mottled liver and red bladder) and histopathological changes noted in the bone marrow (both sexes at  $\geq 10$  mg/kg bw/day), liver (both sexes at  $\geq 10$  mg/kg bw/day), urinary bladder (noted in females at  $\geq 10$  mg/kg bw/day and in males at 30 mg/kg bw/day), kidney (noted in both sexes at 30 mg/kg bw/day) and spleen (noted in both sexes at 30 mg/kg bw/day) (RAR Vol. 3, B.6.3.2.2/01).

### 2-year oral toxicity study in the dog:

In the 2-year oral toxicity study in the Beagle dog, treatment was associated with mortalities noted at 1000 ppm (26.6/29.1 mg/kg bw/day in males and females, respectively) (one male and one female), clinical signs noted at  $\geq$ 250 ppm ( $\geq$ 7.62/6.79 mg/kg bw/day in males and females, respectively) (At 250 ppm: brown-tined urine; At 1000 ppm (26.6/29.1 mg/kg bw/day in males and females, respectively): brown-tined urine, orange stained hair around urogenital area and pale appearing of oral mucosal membranes, a yellowish discoloration of the eyes and

thinness were observed in the female sacrificed in extremis and a general unhealthy appearance characterized by thinness and lethargy was noted in the male sacrificed in extremis), reduced bodyweight growth noted in both sexes at  $\geq 10$  ppm ( $\geq 0.33/0.31$  mg/kg bw/day in males and females, respectively), changes in haematological parameters (indicating anaemia) noted in females at  $\geq 10$  ppm and in males at  $\geq 50$  ppm, changes in biochemical parameters (indicating hepatotoxicity) noted in both sexes at  $\geq 250$  ppm, statistical significant increased organ weight changes (increased lung, spleen, gonads) noted in females at 1000 ppm, changes in gross pathology noted at 10 ppm and above ( $\geq 10$  ppm: urinary bladder;  $\geq 50$  ppm (lung, liver);  $\geq 250$  ppm (spleen, kidney, ovaries) and 1000 ppm (gall bladder, testes, prostate, heart, cartilage, trachea, ribs, tendons, bones, mesenteric lymph nodes, small intestine), and histopathological changes noted in both sexes at  $\geq 50$  ppm.

The haematological changes consisted of following changes: <u>reduced erythrocytes</u> noted in males at 50 (statistically significant week 76 only: 12%), 250 (Week 104: 22%) and 1000 ppm (Week 104: 25%), and in females at 10 (statistically significant week 104 only: 14%), 50 (statistically significant week 104 only: 15%), 250 (Week 104: 27%) and 1000 ppm (Week 104: 51%), <u>reduced haematocrit</u> noted in males at 50 (statistically significant week 76 only: 11%), 250 ppm (17% at Week 76) and 1000 ppm (Week 104: 20%), and in females at 250 ppm Week 104: 15%) and 1000 ppm (Week 104: 43%), <u>reduced haemoglobin</u> noted in males at 250 (Week 76: 12%) and 1000 ppm (Week 104: 24%), and in females at 250 (Week 76: 20%) and 1000 ppm (Week 104: 44%), and <u>increased platelet counts</u> noted in one of the males and in both females of group 1000 ppm at Week 104 (M: 51% n.s.; F: 72%)

The histopathological changes consisted of changes in the adrenals (increased vacuolation of cortical cells noted in both sexes at  $\geq$ 250 ppm (7.62/6.79 mg/kg bw/day in males and females, respectively) and necrosis noted in one female at 1000 ppm (29.1 mg/kg bw/day), lungs (foci of foamy macrophages noted in both sexes at ≥250 ppm, pneumonitis and cholesterol clefts noted in both sexes at 1000 ppm (26.6/29.1 mg/kg bw/day), fibrosis noted in one female at 1000 ppm, edema noted in both sexes at 1000 ppm and consolidation noted in one male at 1000 ppm), <u>spleen</u> (extramedullary haematopoiesis and congestion) noted in females at  $\geq$ 250 ppm and in males at 1000 ppm, liver (At 50 ppm (0.33/0.31 mg/kg bw/day in males and females, respectively): pigment in groups of macrophages (one female), bile plugs in canaliculi (one female); At 250 ppm: pigment in groups of macrophages (females), pigment in kuppfer cells (both sexes), pigment in cytoplasm of hepatocytes (both sexes), bile plugs in canaliculi (one female), bile duct proliferation (both sexes), periportal fibrosis (both sexes), sinusoidal distension (females); At 1000 ppm: pigment in groups of macrophages (both sexes), pigment in kuppfer cells (both sexes), pigment in cytoplasm of hepatocytes (both sexes), bile plugs in canaliculi (both sexes), bile duct proliferation (both sexes), periportal fibrosis (both sexes), sinusoidal distension (females)), urinary bladder (pigment in mucosal cells noted in both sexes at  $\geq$ 50 ppm, pigment laden macrophages noted in females at  $\geq$ 250 ppm and edema noted in one female at 1000 ppm), gall bladder (At 1000 ppm: hyperplasia (both sexes), papillary infolding (both sexes) and choleliths (one female)), kidney (tubular nephrosis noted in one females at 250 ppm and in both sexes at 1000 ppm, healed areas of nephrosis (both sexes) noted at 1000 ppm, dilated renal tubules noted in males at 1000 ppm, cystic tubules (both sexes) noted at 1000 ppm, papillitis noted in one female at 1000 ppm), mesenteric lymph nodes (oedema, erythrophagocytosis and distension of medullary sinuses noted in females at 1000 ppm), pancreas (oedema noted in females at 1000 ppm), testis (focal nonsuppurative orchitis, testicular atrophy and

aspermatogenesis) noted in males at 1000 ppm, and <u>ovaries</u> (lack of cyclic activity, follicular cysts in one animal) noted at 1000 ppm.

In the heart section of one high dose female mineralisation in the coronary arteries as well as in the media and intima of the ank new the base of the heart was noted and considered possibly related to the severe nephropathy. Also this dog had mineralisation of the alveolar wall in the lung as well as a severe dermatitis, ulceration of the oesophagus and erosion in the small intestine.

The reduced bodyweight gain noted in males and females at 10 and 50 ppm were not considered adverse since the body weight gains of the dogs treated at these dose levels were greater than, or comparable to control gains during the first year of the study. Furthermore, the changes in haemotological parameters (reduced erythrocytes) noted in females at 10 ppm were not considered adverse in the absence of other effects on blood at this dose level. Gross pathology changes in urinary bladder (brown mucosa or tan in colour) was not considered adverse in the absence of histopathological findings noted in the urinary bladder at this dose level.

NOAEL for both sexes was set at 10 ppm (0.33 and 0.31 mg/kg bw/day in males and females, respectively) based on mortalities noted in both sexes at 1000 ppm, reduced bodyweight gain noted in both sexes at  $\geq$ 250 ppm, changes in haematological parameters (indicating anaemia) noted in both sexes at  $\geq$ 50 ppm, changes in biochemical parameters (indicating hepatotoxicity) noted in both sexes at  $\geq$ 250 ppm, statistically significant changes in relative organ weights (lung, spleen and gonads) noted in females at 1000 ppm, changes in gross pathology noted at 50 ppm (urinary bladder, spleen, ovary) and 250 ppm (urinary bladder, spleen, liver, ovary, kidneys) and 1000 ppm (urinary bladder, spleen, ovary, liver, gall bladder, kidneys, testes, ovary, heart, lung, mesenteric lymph nodes) and histopathological changes noted in the liver (in females at  $\geq$ 50 ppm; in males at  $\geq$ 250 ppm), urinary bladder (in both sexes at  $\geq$ 50 ppm), adrenals (in both sexes at  $\geq$ 250 ppm), lungs (in both sexes at  $\geq$ 250 ppm), spleen (in males at 1000 ppm; in females at  $\geq$ 250 ppm), kidneys (in both sexes at 1000 ppm), mesenteric lymph node (in females at 1000 ppm), gall bladder (in both sexes at 1000 ppm), pancreas (in females at 1000 ppm), aorta (one female at 1000 ppm), testis (1000 ppm), and ovaries (1000 ppm) (RAR Vol. 3, B.6.3.3.1/01)

### **Rabbit:**

### Teratology study in the rabbit:

Female New Zealand White rabbits were dosed by the oral route with suspensions of ACN Technical (quinoclamine) at doses up to 22.5 mg/kg bw/day. Treatment was associated with maternal reduced bodyweight gain (5%) noted at 22.5 mg/kg bw/day, reduced foetal weight noted at 22.5 mg/kg bw/day (5%. n.s.), increased incidence of skeletal variants (increased number of caudal centra  $\leq$ 15) noted at 22.5 mg/kg bw/day, and malformations noted at 22.5 mg/kg bw/day. The malformations noted at 22.5 mg/kg bw/day included scoliosis (one animal), spina-bifida (three animals), anomalies of the aortic arch (two animals), sternebral fusions (three animals) and hyperextension of limb or paw (one animal). NOAEL for maternal toxicity was 22.5 mg/kg bw/day (highest dose level). NOAEL for developmental toxicity was 7.5 mg/kg bw/day based on increased foetal variations noted at 22.5 mg/kg bw/day centra  $\leq$ 15) noted at 22.5 mg/kg bw/day, and malformations noted at 22.5 mg/kg bw/day based on increased foetal animals variations (increased number of caudal centra  $\leq$ 15) noted at 22.5 mg/kg bw/day based on increased foetal variations (increased number of caudal centra  $\leq$ 15) noted at 22.5 mg/kg bw/day, and malformations noted at 22.5 mg/kg bw/day based on increased foetal variations (increased number of caudal centra  $\leq$ 15) noted at 22.5 mg/kg bw/day, and malformations noted at 22.5 mg/kg bw/day based on increased foetal variations (increased number of caudal centra  $\leq$ 15) noted at 22.5 mg/kg bw/day, and malformations noted at 22.5 mg/kg bw/day.

### 22.5 mg/kg bw/day (RAR Vol. 3, B.6.6.2.2/02).

In the range finding study to the above study, dose levels up to 500 mg/kg bw/day were initially tested. Because of severe toxicity elicited at the highest dose level, doses were reduced after one dose to 8, 20 or 50 mg/kg bw/day. Because mating was staggered over two days, half of the animals in each group received one dose at the initial high dose level and on subsequent days were dosed at the lower level. The other half of the animals in each group received the lowere dose levels throughout the dosing period. Treatment was associated with maternal mortalities noted at 500/50 mg/kg bw/day (both animals died on GD 8), clinical signs noted at  $\geq$ 50 mg/kg bw/day (at 50 mg/kg bw/day: coloured urine, at 80/8 mg/kg bw/day: coloured urine, at 200/20 mg/kg bw/day: coloured urine, at 500/50 mg/kg bw/day (at 50 mg/kg bw/day: 4.5%, at 80/8 mg/kg bw/day: 4%, at 200/20 mg/kg bw/day: 6%, at 500/50 mg/kg bw/day: 12%), reduced food consumption noted at  $\geq$ 20 mg/kg bw/day, increased incidence of post-implantation loss noted at 20 mg/kg bw/day consisted of spina bifida (two animals), interrupted aortic arch major (one animal) and hindlimb left malrotated (one animal). At 50 mg/kg bw/day interrupted aortic arch major (one animal) and kidney left agenesis (one animal) were noted ( RAR Vol. 3, B.6.6.2.2/01)

# Teratology study in the rabbit:

Female Crl.NZW/Kbl BR rabbits were administered quinoclamine orally by gavage at doses up to 30 mg/kg bw/day. Treatment was associated with mortality noted in one dam at 30 mg/kg bw/day (animal kille on day 18 of gestation), reduced maternal bodyweight/bodyweight change noted at 17.5 mg/kg bw/day (bodyweight change Days 12-15: 67% of control) and 30 mg/kg bw/day (reduced body weight Days 4-29: 7%, bodyweight change Days 4-29: 46% of control), reduced maternal food consumption noted at 30 mg/kg bw/day, reduced mean litter size noted at  $\geq 17.5$  mg/kg bw/day, increased post-implantation loss noted at 30 mg/kg bw/day, increased early and late intrauterine deaths noted at 30 mg/kg bw/day, reduced litter weight noted at 30 mg/kg bw/day, increased specific foetal variations noted at 30 mg/kg bw/day and foetal malformations noted at 17.5 mg/kg bw/day (hydronephrosis, abnormal terminal caudal verebrae) and 30 mg/kg bw/day (hydronephrosis, abnormal terminal caudal vertebrae, misshapen nasal bone, misaligned thoracic vertebral arch, absent frontal). The increased incidence of specific foetal variations consisted of: kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior fontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, and asymmetric ossification of cervical vertebral centra. NOAEL for maternal toxicity was 5 mg/kg bw/day based on reduced bodyweight growth noted at 17.5 mg/kg bw/day (bodyweight change Days 12-15: 67% of control) and 30 mg/kg bw/day (bodyweight change Days 4-29: 46% of control), reduced mean litter size noted at  $\geq$ 17.5 mg/kg bw/day, increased post-implantation loss noted at 30 mg/kg bw/day, increased early and late intrauterine deaths noted at 30 mg/kg bw/day, and reduced litter weight noted at 30 mg/kg bw/day. NOAEL for developmental toxicity was 5 mg/kg bw/day based on reduced mean litter size noted at ≥17.5 mg/kg bw/day, increased post-implantation loss noted at 30 mg/kg bw/day, increased early and late intrauterine deaths noted at 30 mg/kg bw/day, reduced litter weight noted at 30 mg/kg bw/day, increased incidence of specific foetal variations noted at 30 mg/kg bw/day, and malformations noted at  $\geq$ 17.5 mg/kg bw/day (RAR Vol. 3, B.6.6.2.2/04).

The second				
Study reference	(mg/kg/day)	Length of exposure	Extrapolated effective dose when extrapolated to 90- day exposure	supported by the study
Anonymous 15 (2002) Report No.: 619/148 28-day oral toxicity study in the rat	500 ppm (44 mg/kg bw/day) (haemolytic anaemia)	28 days	30 <c≤300 kg<br="" mg="">bw/day</c≤300>	STOT-RE Category 2
Anonymous 22 (2002) Report No.: 0619/133 28-day dermal toxicity study in the rat	1000 mg/kg bw/day (tubular degeneration/regeneration in the kidney cortex, hydronephrosis)	28 days	60 <c≤600 kg<br="" mg="">bw/day</c≤600>	-
Anonymous 21 (1976) Report No.: 854/110 2-year feeding study in the dog	250 ppm (6.79 mg/kg bw/day) (haemolytic anaemia, tubular nephrosis)	2 years	2.5 <c≤12.5 kg<br="" mg="">bw/day</c≤12.5>	STOT-RE Category 2
Anonymous 23 (1991) Report No.: AKJ/7/90 104 week feeding study in the rat	50 ppm (3.65 mg/kg bw/day) (renal calcification)	104 weeks	2.5 <c≤12.5 kg<br="" mg="">bw/day</c≤12.5>	STOT-RE Category 2

### Comparison with the CLP criteria regarding STOT RE (specific target organ toxicity-repeated 2.6.3.1.2 exposure)

Regulation EC No 1272/2008 (CLP), Annex 1: 3.9.2.7.3, states for STOT RE:

"All available evidence, and relevance to human health, shall be taken into consideration in the classification process, including but not limited to the following toxic effects in humans and/or animals:

(a) morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites;

(b) significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell): (c) any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters; (d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(e) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

(f) morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver);

(g) evidence of appreciable cell death (including degeneration and reduced cell number) in vital organs incapable of regeneration.

According to the CLP Guidance (Table 3.9.2), a substance should be classified in Category 1 when significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals are seen to occur within the guidance value ranges as indicated in table below:

Route of Exposure	Units	Guidance Values Ranges: (dose/concentration)
Oral (rat)	mg/kg bw/day	C≤10
Dermal (rat or rabbit)	mg/kg bw/day	C≤20
Inhalation (rat) gas	ppm V/6h/day	C≤50
Inhalation (rat) vapour	mg/litre/6h/day	C≤0.2
Inhalation (rat) dust/mist/fume	mg/litre/6h/day	C≤0.2

According to the CLP Guidance (Table 3.9.3), a substance should be classified in Category 2 when significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals are seen to occur within the guidance value ranges as indicated in table below:

Route of Exposure	Units	Guidance Values Ranges: (dose/concentration)
Oral (rat)	mg/kg bw/day	10 <c≤100< td=""></c≤100<>
Dermal (rat or rabbit)	mg/kg bw/day	20 <c≤200< td=""></c≤200<>
Inhalation (rat) gas	ppm V/6h/day	50 <c≤250< td=""></c≤250<>
Inhalation (rat) vapour	mg/litre/6h/day	0.2 <c≤1.0< td=""></c≤1.0<>
Inhalation (rat) dust/mist/fume	mg/litre/6h/day	0.02 <c≤0.2< td=""></c≤0.2<>

According to Annex 1 3.9.2.9.8, the guidance values in tables above is increased by a factor of three for a 28-day study.

The CLP Guidance also states the following for STOT RE (in 3.9.1):

"Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs."

# Rat:

# 28-day oral toxicity study in the rat (RAR Vol. 3, B.6.3.1.1/01)

In this study, rats (CrI:CD<sup>®</sup>(SD)IGSBR) were administered quinoclamine in the diet for 4-weeks at doses up to 1000 ppm (84 and 90 mg/kg bw/day in males and females, respectively). The kidneys, liver and thymus were the apparent target organs in the study. Furthermore, changes in haematological parameters (decreased haemoglobin) in combination with red-,brown-or dark coloured urine and presence of amorphous debris in urine, indicate that quinoclamine causes haemolytic anaemia. Findings in the kidneys consisted of large kidney noted in one male at 1000 ppm (84 mg/kg bw/day) and histopathological changes noted in males at 500 ppm (44 mg/kg bw/day) (increased incidence of eosinophilic hyaline droplets in the cytoplasm of the proximal tubular epithelium) and 1000 ppm (84 mg/kg bw/day) (eosinophilic hyaline droplets in the cytoplasm of the proximal tubular epithelium, minor papillitis characterized by hyperbasophilia of the collecting duct epithelium, interstitial polymorph accumulation and hyperplasia of the urothelium overlying the renal papilla). Effects on the liver consisted of changes in biochemical parameters noted in males at  $\geq$ 500 ppm ( $\geq$ 44 mg/kg bw/day) (decreased alanine aminotransferase) and in females at 1000 ppm (90 mg/kg bw/day) (increased bilirubin). Effects on the thymus consisted of increased adjusted organ weights noted in both sexes at  $\geq$ 500 ppm (44/48 mg/kg bw/day in males and

females, respectively). Changes in haematological parameters were noted in both sexes at  $\geq$ 500 ppm. The magnitude of reduced haemoglobin was up to 13% at the dose level of 1000 ppm. Changes in urine analysis parameters (red-,brown-or dark coloured urine and presence of amorphous debris in urine) were noted in both sexes at  $\geq$ 500 ppm. Increased urine volume was noted in addition in males at 1000 ppm. The changes in blood indicating haemolytic anaemia (reduced haemoglobin at  $\geq$ 10% in combination with red-,brown- or dark coloured urine and presence of amorphous debris in urine) were noted in data coloured urine and presence of amorphous debris or Cat 2 classification (i.e.  $30 < C \leq 300 \text{ mg/kg bw/day}$ ) (Haber's rule considered for exposure duration of 28 days). These effects support a classification of quinoclamine as STOT RE 2 (H373).

# 90-day oral toxicity study in the Sprague-Dawley rat (RAR Vol. 3, B.6.3.2.1/01)

In this study, rats (Sprague-Dawley) were administered quinoclamine in the diet for 13 weeks at doses up to 1000 ppm (62 and 65 mg/kg bw/day in males and females, respectively). The kidneys, liver and spleen were the apparent target organs in the study. The effects on the kidney consisted of increased kidney weights noted in males at 200 ppm (14 mg/kg bw/day) (relative weight of right kidney: 7%) and in both sexes at 1000 ppm (Males: absolute weight: 20%, relative weight: 11%; Females: relative weight: 17%). Furthermore, histopathological changes in the kidney were noted in males at 1000 ppm (62 mg/kg bw/day) (hyaline droplets in the cortical epithelium). The effects on the liver consisted of changes in biochemical parameters noted in males at ≥50 ppm (≥3 mg/kg bw/day) (decreased albumin/globulin ratio), increased liver weights noted in both sexes at 1000 ppm (Males: absolute weight: 12%, relative weight: 16%; Females: relative weight: 19%) and histopathological changes noted in both sexes at 1000 ppm (bile duct proliferation). The effects on the spleen consisted of increased spleen weights noted in both sexes at 1000 ppm (Males: absolute weight: 58%, relative weight: 63%; Females: absolute weight: 18%, relative weight: 35%) and histopathological changes noted in both sexes at 1000 ppm (increased hemosiderin deposition). Effects on the spleen (hemosiderin deposition) were noted within the critical range of doses for Cat 2 classification (i.e.  $10 \le 100 \text{ mg/kg bw/day}$ ) but there were no other changes in this study indicating significant haemolytic anaemia (e.g. a reduction in Hb at  $\geq 10\%$ ). The study was considered limited and only accepted as supportive data.

### 90-day oral toxicity study in the Crl:CD(SD)IGSBR rat (RAR Vol. 3, B.6.3.2.1/02)

In this study, rats (Crl:CD(SD)IGSBR) were administered quinoclamine in the diet for 13 weeks at doses up to 800 ppm (56.74 and 74.81 mg/kg bw/day in males and females, respectively). The kidneys, liver, spleen and thymus were the apparent target organs in the study. Furthermore, changes in haematological parameters (decreased haemoglobin  $\geq$ 10%) in combination with dark straw coloured urine were noted at 800 ppm. The effects on the kidneys consisted of histopathological changes noted in both sexes at 800 ppm (increased extent of eosinoplic hyaline droplets in the cytoplasm of the proximal tubular epithelium in males, increased incidence of pigment in females, increased extent of focal nephropathy in males and females and papillary interstitial eosinophilia noted in males). The effects on the liver consisted of changes in biochemical parameters noted in males at 800 ppm (increased mean aspartate aminotransferase), increased liver weights noted in both sexes at 800 ppm (Males: relative weight: 10%; Females: relative weight: 16%) and histopathological changes noted in both sexes at  $\geq$ 200 ppm (13.89 and 17.81 mg/kg bw/day in males and females, respectively) (sinusoidal cell

pigment). The effects in the spleen consisted of increased spleen weight noted in males at 200 ppm (relative weight: 22%) and in both sexes at 800 ppm (Males: relative weight: 44%; Females: relative weight: 22%), enlarged spleen noted in males at 800 ppm and histopathological changes noted in females at 200 ppm (increased extent of pigment) and in both sexes at 800 ppm (increased incidence of congestion in males and females, increased extent of haemopoiesis in males, and increased extent of pigment in females). The effects on the thymus consisted of reduced thymus weight noted in females at 200 ppm (relative weight 40%) and 800 ppm (relative weight: 48%) and histopathological changes (minor thymic atrophy) noted in both sexes at 800 ppm.

The findings of reduced haemoglobin (>10%) in combination with dark straw coloured urine and effects on the spleen (increased extent of pigment and haemopoiesis) indicate haemolytic anaemia. This effect were considered relevant for human health and noted within the critical range of doses for STOT RE classification in Category 2 (i.e.  $10 < C \le 100 \text{ mg/kg bw/day}$ ). This effect support a classification of quinoclamine as STOT RE 2 (H373).

### Long-term toxicity and carcinogenicity in the rat (RAR Vol. 3, B.6.5.1/01)

In this study, Crl: CD(SD) BR rats were administered quinoclamine orally via the diet for 104 weeks at doses up to 676 ppm (37.6 and 49.4 mg/kg bw/day in males and females, respectively). The kidneys, urinary bladder, lungs, ureter, urethra, parathyroid, pancreas, spleen, thymus, thyroid, heart, adrenal and mammary gland were the apparent target organs in the study. Furthermore, changes in haematological parameters (decreased haemoglobin <10%, red blood cell volume and red blood cell count) were noted at the highest dose level (676 ppm). Effects on the spleen, thyroid, thymus and heart consisted of organ weight changes noted at 676 ppm. The effects on the kidneys consisted of increased relative kidney weights noted in males at  $\geq$ 52 ppm ( $\geq$ 2.82 mg/kg bw/day) and histopathological changes noted in both sexes at  $\geq$ 52 ppm ( $\geq$ 2.82 and  $\geq$ 3.65 mg/kg bw/day in males and females, respectively) (epithelial hyperplasia in both sexes at  $\geq$ 52 ppm, increased incidence of renal calcification in females at  $\geq$ 52 ppm, renal papillary degeneration/necrosis in both sexes at 676 ppm, increased incidence of renal cortical scarring in both sexes at 676 ppm, pelvis polyp noted in one male at 676 ppm).

Effects on the lungs consisted of histopathological changes (arterial calcification) noted in both sexes at 676 ppm and in males at 52 ppm. This effect and the renal calcification in females from the 676 ppm and 52 ppm together with a related small increase in the incidence of parathyroid hyperplasia in terminal kill and decedent high dose males were indicative of alterations in blood calcium levels due to interference in the renal regulation of phosphorus and calcium ions. It is possible that the treatment-related kidney lesions could have affected these excretory mechanism according to study author.

The effects on the urinary bladder consisted of histopathological changes noted in both sexes at  $\geq$ 52 ppm ( $\geq$ 2.82 and 3.65 mg/kg bw/day) (epithelial hyperplasia noted in both sexes at  $\geq$ 52 ppm, benign transitional cell papilloma noted in both sexes at 676 ppm and in males at 52 ppm, polyp noted in one female at 676 ppm and chronic inflammation noted in both sexes at 676 ppm). The benign transitional cell papilloma noted in one single male at 52 ppm was considered of no clear relevance. The polyp seen in the urinary bladder of one high dose terminal kill female probably developed as a response to the irritant toxic effect of the test compound on the urothelium, according to study author.

The effects on the adrenal consisted of increased weight (9%) noted in females at 676 ppm and histopathological changes (benign phaeochromocytoma) noted in both sexes at 676 ppm.

The effects on the ureter and urethra consisted of histopathological changes (epithelial hyperplasia) noted in both sexes at 676 ppm.

Effects on the mammary gland consisted of histopathological changes (reduced mammary acinar development and secretion) noted in females at 676 ppm. This effect was probably related to the reduced food consumption and the lower bodyweight in these high dose animals, according to the study author.

The effect of neoplastic changes in the adrenal (benign phaeochromocytoma) and urinary bladder (benign transitional cell papilloma) was not considered relevant for STOT-RE classification, but for carcinogenicity (section 2.6.5). No adverse reduction in haemoglobin was noted in this study. Effects on the kidneys (increased incidence of calcification) were noted within the critical range of doses for STOT RE 2 (H373) classification (i.e.  $2.5 < C \le 12.5 \text{ mg/kg bw/day}$ ) (Haber's rule considered for exposure durations of 104 weeks).

### Two generation reproduction toxicity study in the rat (RAR Vol. 3, B.6.6.1/01)

In this study, Sprague Dawley rats were administered quinoclamine in the diet at dose level up to 500 ppm (30.9 mg/kg bw/day). The reproductive performance was not affected by quinoclamine treatment. Systemic toxicity for both the parental and the offspring generation comprised a reduction in body weights and bodyweight gains, and reduced litter size was noted at the dose level of 500 ppm. Furthermore, increased incidence of gray lung cysts were noted in F2b generation offspring reared for 3 months. The findings of gray lung cysts in the F2b offspring was dose related although the relevance of this finding is not clear. The finding was not observed in the offspring of the F1b generation reared for 5 weeks or in other available toxicological studies on quinoclamine. The relevance of the effects noted in this study were too unclear for STOT-RE classification.

### Rat developmental toxicity study (RAR Vol. 3, B.6.6.2.1/02)

In this study, female CD rats of Sprague-Dawley origin (CD(SD)BR) were administered quinoclamine orally by gavage during Gestation days 7-17 at doses up to 75 mg/kg bw/day. Adverse maternal findings were noted at 20 mg/kg bw/day (enlarged spleen in one dam) and 75 mg/kg bw/day (enlarged spleen in four dams and reduced bodyweight gain). Developmental effects such as abnormalities (aortic arch malformations) and increased incidence of skeletal variants were noted at  $\geq 20$  mg/kg bw/day. These developmental effects were not considered relevant for STOT-RE classification, but for reproductive toxicity (section 2.6.6). In the absence of data for haematology and histopathology, the findings of enlarged spleen were not considered severe enough for classification as STOT-RE.

### Rat developmental toxicity study (RAR Vol. 3, B.6.6.2.1/04)

In this study, female Crl:CD(SD)IGSBR rats were administered quinoclamine orally by gavage during Gestation days 6-19 at doses up to 75 mg/kg bw/day. Adverse maternal findings were noted at 20 mg/kg bw/day (reduced

bodyweight gain) and 75 mg/kg bw/day (reduced body weight gain/bodyweight loss). Developmental effects such as reduced foetal weight and increased incidence of skeletal variants were noted at  $\geq$ 20 mg/kg bw/day, and malformations were noted at 75 mg/kg bw/day. These effects were not considered relevant for STOT-RE classification, but for reproductive toxicity (section 2.6.6). Nor were the maternal effects noted in the study considered of concern for a classification as STOT-RE since the effects were not severe enough for classification.

### 28-day dermal toxicity study in the rat (RAR Vol. 3, B.6.3.4.1/01)

In this study, Crl:CD:(SD)IGSBR rats were administered quinoclamine by the dermal route for 28 days at doses up to 1000 mg/kg bw/day. The kidney was the apparent target organ for systemic toxicity. The finding in the kidney consisted of histopathological changes noted at 1000 mg/kg bw/day (tubular degeneration/regeneration in the kidney cortex noted in one animal of each sex and hydronephrosis and pigment noted in one female). The effects noted in the study were not considered of concern for a classification as STOT-RE since no adverse effects were noted within the critical range of doses for STOT RE 2 (H373) classification (i.e.  $60 < C \le 600$  mg/kg bw/day) (Haber's rule considered for exposure duration of 28 days).

### Mouse:

### 80-week carcinogenicity study in the mouse (RAR Vol 3, B.6.5.2/01)

In this study, Crl:CD-1 (ICR)BR mice were administered quinoclamine orally via the diet for 80 weeks at doses up to 300 ppm (40.2 and 46.4 mg/kg bw/day in males and females, respectively). The kidney, adrenal, urinary bladder, urether, spleen, stomach, liver, heart, sciatic nerve, lymph nodes and lympho reticular tissue were the apparent target organs. Furthermore, increased mortalities were noted in both sexes at  $\geq$ 30 ppm  $(\geq 3.82 \text{ and } \geq 4.48 \text{ mg/kg bw/day in males and females, respectively})$ . It could however be noted that the mortality in the study was exceptionally low and only at the highest dose level (300 ppm) did mortality approach the levels expected in comparison to historical control data (-50%). The findings in the liver consisted of increased liver weight and histopathological changes noted in females at 300 ppm (46.4 mg/kg bw/day) (chronic inflammation and brown pigmentation). In the adrenal, histopathological changes were noted in females at 30 ppm (4.48 mg/kg bw/day) (adrenal spindle cell hyperplasia and brown athrophy) and in both sexes at 300 ppm (increased incidence of adrenal spindle cell hyperplasia noted in males and brown athrophy noted in females). The findings in the heart consisted of increased relative organ weight and histopathological changes (generalised periarteritis and myocardial fibrosis) noted in females at 300 ppm, and histopathological changes of myocardial fibrosis noted in males at the same dose level. In addition at 300 ppm, histopathological changes were noted in the kidneys (cortical scarring and hydronephrosis. both sexes), spleen (increased incidence of adrenal spindle cell hyperplasia and brown athropy, males only), urether (dilation, both sexes), urinary bladder (epithelial hyperplasia, particularly in females), stomach (hyperkeratois, both sexes), lymph nodes (histiocytosis, both sexes) and sciatic nerve (degeneration, females). The effects noted in the study were not considered of concern for a classification as STOT-RE. No effects of significant toxicity were noted within the critical range of doses for Cat 2 classification (i.e.  $1.5 \le C \le 15$  mg/kg bw/day) (Haber's rule considered for exposure duration of 80 weeks).

The effect of neoplastic changes (malignant lymphoma) was not considered relevant for STOT-RE classification, but for carcinogenicity (section 2.6.5).

# Rabbit:

### Rabbit developmental toxicity study (RAR Vol. 3, B.6.6.2.2/02)

In this study, female New Zealand rabbits were administered quinoclamine orally by gavage during Gestation Days 6-18 at doses up to 22.5 mg/kg bw/day. No adverse maternal effects were noted. Developmental effects such as increased incidence of skeletal variants were noted at 22.5 mg/kg bw/day. These effects were not considered relevant for STOT-RE classification, but for reproductive toxicity (section 2.6.6).

In the range finding study to the study above (RAR Vol. 3, B.6.6.2.2/01), female New Zealand White rabbits (5/group) were administered Quinoclamine orally by gavage during Gestation Days 6-18. Dose levels up to 500 mg/kg bw/day were initially tested. Because of severe toxicity elicited at the highest dose level, doses were reduced after one dose to 8, 20 or 50 mg/kg bw/day. Because mating was staggered over two days, half of the animals in each group received one dose at the initial high dose level and on subsequent days were dosed at the lower level. The other half of the animals in each group received the lowere dose levels throughout the dosing period. Maternal mortalities were noted in both animals exposed at 500/50 mg/kg bw/day (one animal died on Day 9 and the other on Day 10 of pregnancy) but no deaths were noted at 50 mg/kg bw/day. At necropsy these animals showed pale liver, abnormal spleen and dark intestinal contents. The mortalities noted in the study occurred after 3 to 4 days following administration, and could be considered as an acute effect rather than an effect of repeated administration.

### Rabbit developmental toxicity study (RAR Vol. 3, B.6.6.2.2/04)

In this study, female Crl.NZW/Kbl BR rabbits were administered quinoclamine orally by gavage during Gestation days 7-28 at doses up to 30 mg/kg bw/day. Adverse maternal findings were noted at 17.5 mg/kg bw/day (reduced bodyweight change) and 30 mg/kg bw/day (mortality, one female killed on Day 18 of gestation, reduced bodyweight change). Developmental effects such as increased incidence of specific foetal variations and malformations were noted at 22.5 mg/kg bw/day. The developmental effects were not considered relevant for STOT-RE classification, but for reproductive toxicity (section 2.6.6).

Mortality was noted in this study in one dam (killed on Day 18 of gestation). This animal showed severe inappetence and body weight loss and clinical observation of red discharge from the urogenital region. Necropsy examination did not reveal any macroscopic abnormalities. Except for this animal, there were no adverse effects of treatment on clinical observations or necropsy findings. The single case of mortality noted in this study was considered of no clear relevance for classification.

### Dog:

# 28-day oral toxicity study in the dog (RAR Vol. 3, B.6.3.1.2/01)

In this study, Beagle dogs were administered Quinoclamine by oral capsules for 28 days at dose levels of 3, 10, 30 and 100 mg/kg bw/day. The high dose animals were removed from the study on Day 5 due to body weight loss and poor clinical condition. The kidneys, urinary bladder, spleen, and liver were the apparent target organs. Increased organ weights (absolute and relative) were noted in both sexes for the spleen (at  $\geq$ 30 mg/kg bw/day) and for the liver (at 100 mg/kg bw/day). Findings in the kidneys consisted of increased absolute and relative kidney weights and histopathological changes (tubular nephropathy and transitional cell hyperplasia) noted in both sexes at 100 mg/kg bw/day. Findings in the urinary bladder consisted of histopathological changes noted at 100 mg/kg bw/day (transitional cell hyperplasia and arteritis noted in both sexes and epithelial necrosis noted in males). The findings of tubular nephropathy in the kidney and epithelial necrosis in the urinary bladder were noted at a dose level expecting to cause lethality. These effects were not observed at the dose level of 30 mg/kg bw/day or in the 90-day oral toxicity study in the dog using doses up to 30 mg/kg bw/day. The relevance of the effects noted at 100 mg/kg bw/day were not considered clear for classification.

# 90-day oral toxicity study in the dog (RAR Vol. 3, B.6.3.2.2/01)

In this study, Beagle dogs were administered Quinoclamine by oral capsules for 90 days at doses up to 30 mg/kg bw/day. The bone marrow, spleen, liver, kidneys, urinary bladder and thyroid/parathyroid were the apparent target organs. Furthermore, changes in haematological parameters were noted in both sexes at ≥10 mg/kg bw/day (including changes such as reduced haemoglobin (>10%) noted at 30 mg/kg bw/day, reduced red blood cell count noted at  $\geq 10 \text{ mg/kg bw/day}$  and increased reticulocyte count noted at  $\geq 10 \text{ mg/kg bw/day}$ ). Increased adjusted thyroid/parathyroid organ weights were noted for males at  $\geq 10$  mg/kg bw/day. The histopathological findings noted in the bone marrow consisted of haemopoiesis characterised by greater cellularity noted in both sexes at  $\geq 10 \text{ mg/kg bw/day}$ . The findings in the spleen consisted of macroscopical changes (enlarged spleen) noted in two females at 30 mg/kg bw/day and histopathological changes (haemopoiesis characterised by increased haemopoietic cells in the red pulp and congestion of the splenic red pulp) noted in both sexes at 30 mg/kg bw/day. The findings in the liver consisted of increased adjusted liver weights noted in females at 10 mg/kg bw/day and in both sexes at 30 mg/kg bw/day. Furthermore, histopathological changes were noted in the liver in both sexes at  $\geq 10$  mg/kg bw/day (sinusoidal cell pigment characterised by presence of intracytoplasmic iron-containing pigment noted at  $\geq 10 \text{ mg/kg bw/day}$  and bile duct hyperplasia noted at 30 mg/kg bw/day). The findings in the urinary bladder consisted of histopathological changes noted at 10 mg/kg bw/day (cystitis in one female) and at 30 mg/kg bw/day (transitional cell hyperplasia noted in both sexes, arteritis in one male, and cystitis in one female). At 30 mg/kg bw/day, histopathological changes were also found in the kidneys (pigment noted in both sexes).

In this study, there was increased haemopoiesis in the bone marrow and spleen together with the increase in ironcontaining pigment in the liver, this was indicative for low grade haemolytic anaemia and correlated with the findings of reduced red blood cell count and haemoglobin concentration (>10%) and increased reticulocyte count observed in the intermediate (10 mg/kg bw/day) and high dose groups (30 mg/kg bw/day). These findings were considered of significant toxicity for STOT-RE classification. The effects were considered severe and relevant for human health and noted within the critical range of doses for STOT RE 2 (H373) classification (i.e.  $10 < C \le 100$  mg/kg bw/day).

### 2-year oral toxicity study in the dog (RAR Vol. 3, B.6.3.3.1/01)

In this study, Beagle dogs were administered Quinoclamine in the diet for two years at doses up to 1000 ppm (26.6 and 29.1 mg/kg bw/day in males and females, respectively). The kidneys, spleen, liver, gall bladder, urinary bladder, lung, testes, prostate, ovary, adrenal gland, heart, mesenteric lymph nodes, pancreas and small intestine were the apparent target organs. Furthermore, changes in haematological parameters were noted in females at  $\geq$ 10 ppm ( $\geq$ 0.31 mg/kg bw/day) and in males at  $\geq$ 50 ppm ( $\geq$ 1.42 mg/kg bw/day). Changes in haematological parameters included changes such as reduced haemoglobin noted in both sexes at 250 ppm (7.62 and 6.79 mg/kg bw/day in males and females, respectively) (>10%) and 1000 ppm (>20%), reduced erythrocytes noted in females at  $\geq$ 10 ppm (0.31 mg/kg bw/day) and in males at  $\geq$ 50 ppm (1.42 mg/kg bw/day), and reduced haematocrit noted in males at  $\geq$ 10 ppm (0.31 mg/kg bw/day) and in males at  $\geq$ 50 ppm (1.42 mg/kg bw/day).

Treatment related mortalities were noted at 1000 ppm (26.6 and 29.1 mg/kg bw/day in males and females, respectively) (one animal of each sex sacrificed in extremis during week 65). Pale appearing oral mucosal membranes were observed in all high dose group animals, a yellowish discoloration of the eyes and thinness were observed in the 1000 ppm group female sacrificed in extremis, and a general unhealthy appearance characterized by thinness and lethargy was noted in the group 1000 ppm male sacrificed in extremis.

The findings in the kidneys consisted of histopathological changes noted at 250 ppm (6.79 mg/kg bw/day) (tubular nephrosis noted in one female) and 1000 ppm (26.6 and 29.1 mg/kg bw/day in males and females, respectively) (tubular nephropathy with fibrosis and renal tubular regeneration noted in both sexes). Furthermore, macroscopical changes in the kidneys were noted at 250 ppm (7.62 and 6.79 mg/kg bw/day in males and females, respectively) (depressed areas on surface) and 1000 ppm (small, depressed areas on surface, contracted, polycystic- primarily in the medulla, cortex collapsed, thickened and opaque areas on capsule). The histopathological findings in the spleen consisted of extramedullary haematopoiesis and congestion noted in females at ≥250 ppm (≥6.79 mg/kg bw/day) and in males at 1000 ppm (26.6 mg/kg bw/day). Furthermore, macroscopical changes in the spleen were noted at 50 ppm (1.42 and 1.39 mg/kg bw/day in males and females, respectively) (dark in colour or margins dark) and 1000 ppm (26.6 and 29.1 mg/kg bw/day in males and females, respectively) (dark in colour or margins dark, enlarged), and increased relative spleen weight was noted in females at 1000 ppm (29.1 mg/kg bw/day).

The findings in the adrenal consisted of histopathological changes noted at 250 ppm (7.62 and 6.79 mg/kg bw/day in males and females, respectively) (increased vacuolation of cortical cells noted in both sexes, focal nonsupparative adrenalitis noted in one male) and 1000 ppm (26.6 and 29.1 mg/kg bw/day in males and females, respectively) (increased vacuolation of cortical cells noted in both sexes, and necrosis noted in one female). The findings in the liver consisted of histopathological changes noted at 50 ppm (1.39 mg/kg bw/day) (pigment in macrophages noted in one female and bile plugs in canaliculi noted in one female), 250 ppm (7.62 and 6.79 mg/kg

bw/day in males and females, respectively) (pigment in cytoplasm of hepatocytes and Kuppfer cells noted in both sexes, pigment in macrophages noted in females, periportal fibrosis noted in both sexes, bile duct proliferation noted in both sexes, bile plugs in canaliculi noted in one female, sinusoidal distension noted in females) and 1000 ppm (26.6 and 29.1 mg/kg bw/day in males and females, respectively) (pigment in cytoplasm of hepatocytes, Kuppfer cells and macrophages noted in both sexes, periportal fibrosis noted in both sexes, bile duct proliferation noted in both sexes, bile plugs in canaliculi noted in both sexes and sinusoidal distension noted in females). Furthermore, macrosopical changes in the liver were noted at 250 ppm (brown in colour, rough surfaced, tough in consistency, firm) and 1000 ppm (enlarged lobes, thickened and pale, rough surfaced and motted, brown in colour, tough in consistency, firm). Changes in biochemical parameters also indicated liver toxicity (increased serum glutamic-pyruvic transaminase noted in both sexes at ≥250 ppm, increased alkaline phosphatase noted in both sexes at ≥250 ppm, and increased serum glutamic-oxaloacetic transaminase noted in both sexes at ≥250 ppm, and increased bilirubin noted in females at 1000 ppm).

The findings in the gall bladder consisted of macroscopical changes noted at 1000 ppm (26.6 and 29.1 mg/kg bw/day in males and females, respectively) (distended, walls thickened) and histopathological changes noted at 1000 ppm (hyperplasia noted in both sexes, papillary infolding noted in both sexes, cholelith noted in one female). The findings in the urinary bladder consisted of histopathological changes noted at 50 ppm (1.42 and 1.39 mg/kg bw/day in males and females, respectively) (pigment in mucosal cells noted in both sexes), 250 ppm (pigment in mucosal cells noted in both sexes, pigment laden macrophages noted in females) and 1000 ppm (26.6 and 29.1 mg/kg bw/day in males and females, respectively) (pigment in mucosal cells noted in both sexes, oedema noted in one female, pigment laden macrophages noted in one female). Furthermore, macroscopical changes were noted in the urinary bladder at 10 ppm (0.33 and 0.31 mg/kg bw/day in males and females, respectively) (mucosa brown or tan in colour), 50 ppm (mucosa brown or tan in colour), 250 ppm (mucosal surface brown or yellowgray) and 1000 ppm (brown mucosa or tan in colour, wall thickened, omentum adhered to serosal surface). The findings in the lungs consisted of histopathological changes noted at 50 ppm (1.42 mg/kg bw/day) (focal pneumonitis noted in one male) and 250 ppm (foci of foamy macrophages noted in both sexes) and 1000 ppm (foci of foamy macrophages noted in both sexes, focal pneumonitis noted in both sexes, cholesterol clefts noted in both sexes, fibrosis noted in one female, oedema noted in both sexes, consolidation noted in one male). Furthermore, macroscopical changes were noted in the lungs at 250 ppm (white foci on surface) and 1000 ppm (raised yellow gray foci on all lobes, focal emphysematous appearing areas).

The findings in the mesenteric lymph nodes consisted of histopathological changes (oedema, erythrophagocytosis, distension of medullary sinuses in females) and macroscopical changes (dark in colour) noted at 1000 ppm. The findings in the pancreas consisted of histopathological changes (oedema) noted in females at 1000 ppm (29.1 mg/kg bw/day).

Findings in the heart were also noted, and consisted of histopathological changes (mineralisation noted in one female) and macroscopical changes (reddish-brown discoloration at coronary grove, right A/V valve thickened and vascular with dark raised area near point of attachment at week 52) noted at 1000 ppm. The findings in this female was considered possibly related to the severe nephropathy noted in this animal. Also this dog had mineralisation of the alveolar wall in the lung as well as a severe dermatitis, ulceration of the oesophagus and erosion in the small intestine.

In addition to the toxic changes described above, macroscopic changes were noted in the following organs: cartilage (yellow to brown in colour), trachea (brown or gray discoloration), ribs (brown of gray discoloration), tendons (brown or gray discoloration), bones (gray in colour) at 1000 ppm.

There were findings indicative of anaemia, characterized by decreased haemoglobin. At 250 ppm (7.62/6.79 mg/kg bw/day in males and females, respectively) haemoglobin was reduced >10%. At 1000 ppm (26.6/29.1 mg/kg bw/day in males and females, respectively) haemoglobin was reduced >20% and pale mucosal membranes were noted. Histomorphological changes of extramedullary haematopoesis and congestion were noted in the spleen at  $\geq$ 250 ppm and pigmentation of urinary bladder was noted at  $\geq$ 50 ppm. There were also clear evidence of marked organ dysfunction in the kidney. The marked organ dysfunction in the kidney consisted of tubular nephrosis noted in one female at 250 ppm (6.79 mg/kg bw/day) and tubular nephropathy with fibrosis and renal tubular regeneration noted in both sexes at 1000 ppm (26.6/29.1 mg/kg bw/day in males and females, respectively). These findings were considered of significant toxicity for STOT-RE classification. The effects were considered severe and relevant for human health and noted within the critical range of doses for STOT RE 2 (H373) classification (i.e. 2.5<C≤12.5 mg/kg bw/day) (Haber's rule considered for exposure duration of 2 years).

### **Overall conclusion- findings relevant for STOT-RE:**

There were **no** significant toxic effects observed in the available studies at or below the guidance values (Table 3.9.2 of Annex I: 3.9.2.9.6 to the CLP Regulation) that would support classification of quinoclomaine as STOT RE 1 (H372).

In the oral 28-day rat study (CD rat), changes in blood indicating haemolytic anaemia (reduced haemoglobin at  $\geq$ 10% in combination with red-,brown- or dark coloured urine and presence of amorphous debris in urine) were noted at the dose level of 44 mg/kg bw/day. The effects were noted within the critical range of doses for STOT RE classification in Category 2 (i.e. 30<C≤300 mg/kg bw/day). The effects noted support a classification of quinoclamine as STOT RE 2 (H373).

In the 90-day oral toxicity study (CD rat), findings of reduced haemoglobin at (>10% in combination with dark straw colored urine, indicating haemolytic anaemia, were noted at the dose level of 56.74 mg/kg bw/day. The effects were considered relevant for human health and noted within the critical range of doses for STOT RE classification in Category 2 (i.e.  $10 < C \le 100$  mg/kg bw/day). The effects noted support a classification of quinoclamine as STOT RE 2 (H373).

In the 90-day oral toxicity study (Sprague Dawley rat), hemosiderin deposition was noted in the spleen at the dose level of 62 mg/kg bw/day. This effect indicate haemolytic anaemia, although there were no adverse reduction in haemoglobin noted in this study. The study was considered limited and accepted as supportive data only.

In the 28-day oral toxicity study in the dog, epithelial necrosis was noted in the urinary bladder of males at the dose level of 100 mg/kg bw/day after five days exposure. Body weight loss and poor clinical condition were also noted in these animals and all animals in the dose group were removed from the study on Day 5. Furthermore, effects on the kidneys (tubular nephropathy) were noted at this dose level after five days exposure. The findings of tubular nephropathy in the kidney and epithelial necrosis in the urinary bladder were noted at a dose level expecting to cause lethality. These effects were not observed at the dose level of 30 mg/kg bw/day or in the 90-day oral toxicity study in the dog using doses up to 30 mg/kg bw/day. The relevance of the effects noted at 100 mg/kg bw/day were considered equivocal for classification.

In the 90-day oral toxicity study in the dog, increased haemopoiesis in the bone marrow and spleen were noted together with the increase in iron-containing pigment in the liver, this was indicative for low grade haemolytic anaemia and correlated with the findings of reduced red blood cell count and haemoglobin concentration (>10%) and increased reticulocyte count observed in the intermediate (10 mg/kg bw/day) and high dose groups (30 mg/kg bw/day). The effects were considered severe and relevant for human health and noted within the critical range of doses for STOT RE 2 (H373) classification (i.e.  $10 < C \le 100$  mg/kg bw/day).

In the 2-year feeding study in the dog, there were findings indicative of anaemia, characterized by decreased haemoglobin (>10% reduction) at the dose level of 6.79 mg/kg bw/day, pale mucosal membranes noted at 26.6 mg/kg bw/day and pigmentation of urinary bladder noted at 1.39 mg/kg bw/day. Histomorphological changes of extramedullary haematopoesis and congestion were also noted in the spleen at the dose level of 6.79 mg/kg bw/day. There were also clear evidence of marked organ dysfunction in the kidney. The marked organ dysfunction in the kidney consisted of tubular nephrosis noted in one female at 6.79 mg/kg bw/day and tubular nephropathy with fibrosis and renal tubular regeneration noted at a dose level of 26.6 mg/kg bw/day. The effects noted were considered severe, and relevant for human health, and noted within the critical range of doses for STOT RE 2 (H373) classification (i.e.  $1.25 < C \le 12.5$  mg/kg bw/day) (Haber's rule considered for exposure duration of 2 years).

In the developmental toxicity study in the rabbit (exposure duration 21 days), a single case of maternal mortality (one dam killed on Day 18 of gestation). This animal showed severe inappetence and body weight loss and clinical observation of red discharge from the urogenital region. Necropsy examination did not reveal any macroscopic abnormalities. Except for this animal, there were no adverse effects of treatment on clinical observations or necropsy findings. The single case of mortality noted in this study was considered of no clear relevance for classification.

# 2.6.3.1.3 Conclusion on classification and labelling for STOT RE (specific target organ toxicity-repeated exposure)

Classification in **STOT RE 2, H373** ("May cause damage to blood system and kidney through prolonged or repeated exposure") is proposed based on findings indicating haemolytic anaemia noted in the dog (90-day and

2-year studies), supported by findings on blood noted in the rat (28-day and 90-day studies), and findings in the kidney (tubular nephrosis) noted in the dog (2-year study). Since no information is available from the repeated dose studies where the inhalation route had been used no route could be specified.

# 2.6.4 Summary of genotoxicity / germ cell mutagenicity

1 abic 2.0.4-1. 5u	Initially table of get			De
Method,	Test substance	Relevant	Observations / Results	Reference
guideline,		information about		
deviations if		the study including		
any		rationale for dose		
		selection (as		
D ( 1		applicable)		DAD V 1 2
Bacterial	Quinoclamine	<u>Tester strain(s):</u>	Quinoclamine did not induce increases in the	RAR Vol. 3, $D \in A 1/01$
reverse	Purity: 99%	Salmonella	number of revertant colonies of any strain at	B.6.4.1/01
mutation test		typhimurium	any dose that was both dose-related and	D
(Ames test)		TA100	reproducible. Quinociamine was non-	Beevers
OECD TC 471		TA1535	mutagenic.	(2002)
OECD IG 4/1		TA153/		N. L.
		TA98	Evidence of toxicity was apparent in all strains	New data
CLD V		Escherichia coli	at the highest one, two or three test doses in $\Gamma$	for the
GLP: Yes		WP2uvrA	Experiment 1 (12.5, 50 and/or 200 µg/plate).	Annex I
				renewal: No
		Concentrations:	In Experiment 2, toxic signs were observed at	
		E	the highest one of two test doses in several of	
		Experiment 1 (All	the test strains.	
		$\underline{\text{strains}}$ : 0.1953-200	The maximum test does (100 us/plate) used for	
		$\mu g/\text{prate}(-5-9 \text{ and } -5-0)$	The maximum test dose (100 $\mu$ g/plate) used for Experiment 2 treatments of strain TA1527 in	
		9)	the presence of S 0 did not induce any	
		Experiment 2:	indications of toxicity in this strain. However	
		$\frac{\text{Experiment 2.}}{\text{TA 08.0 7812 25}}$	it did resulted in a small increase in revertant	
		$\frac{1A 90.0.7013-23}{\mu g/plate}$	numbers. A further treatment of TA1537 was	
		µg/plate (-3-9)	therefore performed at a revised maximum test	
		TA100 TA1527	dose of 100 ug/plate. As a result no increase in	
		$\frac{1A100, 1A1337}{WP2uvrA \cdot 1.563.50}$	revertant numbers was noted at the dose of 100	
		$\frac{\text{wr} 2\text{uvr}A}{\text{ug}/\text{plate}(S,0)}$	ug/plate	
		µg/plate (-3-9)	µg/plate.	
		TA 1535: 3 125-100		
		ug/plate(-S-9)		
		μg/plate (-5-))		
		TA98 TA100		
		TA1537: 1 563-50		
		$\mu g/nlate (+S-9)$		
		µg/plate (15-7)		
		TA1535 WP2uvr		
		$3 125-100 \mu g/plate$		
		(+S-9)		
		ug/plate (+S-9)		
		ng plate (15 ))		
Mammalian	Ouinoclamine	Target cells:	Negative in absence of S-9 nix	RAR Vol. 3.
Chromosome	Purity: not stated	Human lymphocytes		B.6.4.1/02
Aberration	in study report		Positive in presence of S-9 nix at 9 and 18	
Test	Jan	Concentrations:	µg/mL	Asquith
		1.125, 2.25, 4.5 and 9		(1987)
OECD TG 473		µg/ml without S-9		× /

Table 2.6.4-1. Summary table of genotoxicity/germ cell mutagenicity tests in vitro

Mathad	Test aphator as	Delevent	Observations (Desults	Doforma
Mietnoa,	Test substance	kelevant	Observations / Results	Reference
guidenne,		information about		
deviations if		the study including		
any		rationale for dose		
		selection (as		
		applicable)		
GLP: Yes		and 2.25, 4.5, 9 and		New data
		18 µg/ml with S-9		for the
				Annex I
				renewal: No
Mammalian	ACN Technical	Target cells:	ACN (Quinoclamine) did not cause mutations	RAR Vol. 3,
Cell Gene	(Quinoclamine)	L5178 mouse	resistant to Ouabain in L5178Y cells in either	B.6.4.1/03
Mutation Test		lymphoma	the absence or presence of S-9.	
	Purity: 98.1%		-	Asquith
OECD TG 476	-	Concentrations:		(1989)
		Mutation experiment		New data
GLP: Yes		1:		for the
		-S-9 mix: 0.15, 2.5,		Annex I
		$10 \mu g/mL$		renewal: No
		+S-9 mix: 0.4. 2. 8.		
		$30 \mu g/mL$		
		Mutation experiment		
		2:		
		-S-9 mix: 0.15.		
		0.0625, 2.5, 10		
		ug/mL		
		+S-9 mix: 0.4, 2, 8		
		30 µg/mL		
		50 µg/mL		I

# Table 2.6.4-2. Summary table of genotoxicity/mutagenicity tests in mammalian somatic or germ cells in vivo

Method,	Test substance	Relevant	Observations/Results	Reference
guideline,		information		
deviations if		about the study		
any		(as applicable)		
Micronucleus	ACN Technical	Target cells:	ACN (Quinoclamine) did	RAR Vol. 3,
test in mouse	(Quinoclamine)	Mouse bone	not induce micronuclei in	B.6.4.2/01
		marrow	mouse bone marrow cells	
OECD TG	Purity: 98.1%			Anonymous 31 (1989)
474		Mice of both	The study is limited since	
		sexes (LACA	bone marrow exposure was	New data for the Annex I renewal: No
Deviation:		strain)	not shown in the study	
1000				
polychromatic		Dose levels:		
erythrocytes		125, 250 and		
were counted		500 mg/kg		
instead of				
2000		Single		
		intraperitoneal		
GLP: Yes		injection		
Unscheduled	Quinoclamine	Target cells:	No induction of UDS in	RAR Vol. 3,
DNA		Rat liver	hepatocytes was noted in	B.6.4.2/02
Synthesis	Purity: 97.6%		this study.	
(UDS) in rat		Male		Anonymous 32 (1996)
liver		Crl:CD®BR rats	Negative results in the in	
			vivo UDS test are not	New data for the Annex I renewal: No
OECD TG		Dose levels:	considered sufficient to	
486		800 or 2000	overrule positive results in	
		mg/kg		
Method, guideline, deviations if any	Test substance	Relevant information about the study (as applicable)	Observations/Results	Reference
---	----------------	---	--	-----------
GLP: Yes		Single oral dose (gavage)	either of the in vitro gene mutation test	

#### Table 2.6.4-3. Summary table of human data relevant for genotoxicity / germ cell mutagenicity

Type of	Test	Relevant information about the	Observations	Reference
data/report	substance	study (as applicable)		
No data				

# 2.6.4.1 Short summary and overall relevance of the provided information on genotoxicity / germ cell mutagenicity

The genotoxic potential of quinoclamine was investigated in three standard *in vitro* test systems (Ames test, mammalian chromosome aberration test and mammalian cell gene mutation test) and in two *in vivo* tests (*in vivo* mouse micronucleus test and *in vivo* UDS test). All these studies were conducted in accordance with the OECD Principles of Good Laboratory Practice (1981).

All tests were negative except the *in vitro* cytogenetic assay in human lymphocytes (*in vitro* chromosome aberration test) that was positive in the presence of metabolic activation. The in vivo micronucleus test in the mouse was considered limited, since bone marrow exposure was not shown in the study and no measurement of the plasma or blood levels of the test substance was included in the study. Since no ADME data using the same route and the same species are available in the dossier, a **data gap** is identified for *in vivo* genotoxicity.

An *in vivo* UDS test is available. However, the negative results in the *in vivo* UDS test are not considered sufficient to overrule positive results in either of the *in vitro* gene mutation test (EFSA technical report (2016). Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology, EFSA Supporting publication 2016:EN-1074).

No photomutagenicity study is available. However, quinoclamine has been shown to be negative in a standard *in vitro* phototoxicity study (Vol. 3, B.6.2.7/01). Thus, no photomutagenicity study is required.

#### 2.6.4.2 Comparison with the CLP criteria regarding genotoxicity / germ cell mutagenicity

No comparison with the CLP criteria regarding genotoxicity/germ cell mutagenicity has been conducted since a data gap is identified for genotoxicity *in vivo* (see section 2.6.4.1).

# 2.6.4.3 Conclusion on classification and labelling for genotoxicity / germ cell mutagenicity

No conclusion on classification and labelling for genotoxicity/germ cell mutagenicity could be drawn because the data were inconclusive. A data gap is identified for genotoxicity *in vivo*.

# 2.6.5 Summary of long term toxicity and carcinogenicity

Math a	Test and stores	Demolt	Deferment
Method,	lest substance,		Reference
guideline,	dose levels	- NOAEL/LOAEL	
deviations if any,	duration of	- target tissue/organ	
species, strain,	exposure	- critical effects at the LOAEL (bold text)	
sex, no/group			
Long-term toxicity	ACN technical	<u>4 ppm:</u>	RAR Vol. 3,
and carcinogenicity	(Quinoclamine)	-changes in urinalysis (yellow/brown or orange colour)	B.6.5.1/01
		(M, F))	
Oral (dietary)	Purity: 98.3%		Anonymous 23 (1991)
		<u>52 ppm:</u>	
No guideline	Carcinogenicity	-changes in urinalysis (yellow/brown or orange	Report No.: AKJ/7/90
claims presented in	groups:	discoloration) (M, F)	_
study report	0, 4, 52, 676 ppm	-changes in organ weights (Week 27: ↑kidney (M:	
2 1	corresponding to	8%))	New data for the Annex I
	0. 0.21. 2.82.	-histopathological changes in urinary bladder	renewal: No
Rat	37.6 mg/kg	(epithelial hyperplasia (M, F), kidneys (epithelial	
	bw/day in males	hyperplasia (M E) $\uparrow$ renal focal calcification (E)	
Crl·CD(SD)BR	and 0, 0, 28, 3, 65	ureter (epithelial hyperplasia (M F) lungs (arterial	
en.eb(bb)bh	49.4  mg/kg	calcification (M))	
50/sex/group	hw/day in		
50/sex/group	females	676 ppm;	
Study was shocked	lemales	olinical signs (orange fur steining lineidence of mass	
for compliance	Chronic	-children signs (orange fur stanning, $\downarrow$ incluence of mass	
<i>jor compliance</i>	<u>Chronic</u>	beaming annuals) ( $W$ , $F$ )	
with OECD IG	toxicology	$\downarrow$ <b>Dw gain</b> (toxicology evaluation: F: 28%;	
453 and following	groups:	carcinogenicity evaluation: F: 27%)	
deviations were	0, 4, 52, 676 ppm	$\downarrow$ FC (M, F)	
noted:	corresponding to	-changes in haematological parameters (Upacked	
i. Haematological	0, 0.21, 2.89,	blood cell volume (M week 27, 79; F week 53),	
examination was	38.3 mg/kg	↓haemoglobin (M: 8% week 27, F 5% week 27,	
not carried out at 3	bw/day in males;	9% week 53), $\downarrow$ red blood cell count (M week 27, 79;	
months (the	0, 0.28, 3.72,	F: week 27, 53))	
guideline	51.5 mg/kg	-changes in biochemical parameters ( <i>†blood</i> urea	
recommends	bw/day in	nitrogen (M n.s., F n.s.), \calcium (M: week 27, 79; F:	
measurements at 3	females	n.s.), ↓inorganic phosphorous (M: n.s, F: week 27, 53),	
months if effect was		↓lactate dehydrogenase (M: week 79, 103; F: week	
seen on	104 weeks	103))	
haematological		-changes in organ weights (Week 27: 1 rel kidney (M:	
parameters in a		15%), ↑adrenals (F: 38%), <u>Week 53</u> : ↑kidney (M:	
previous 90 day		10%), <u>Week 79:</u> ↑heart (M: 18%, F: 28%), ↑brain (F:	
study)		28%), ↑spleen (F. 13%), ↑kidney (F: 19%), Week 104:	
ii. Prothrombin		↑brain (F: 23%), ↑thyroid (F:43%), ↑(heart (F: 16%),	
time and activated		↑adrenals (F: 9%), ↑thymus (F: 50%))	
partial		-changes in urinalysis (yellow/brown or orange	
thromboplastin		discoloration (M, F), diuretic animals (M))	
time was not		-macroscopical changes in urinary bladder (orange	
investigated		discoloration of the urinary bladder serosa) (M, F) and	
iii. Urea was not		skin (orange staining (M, F))	
investigated		-histopathological changes in urinary bladder (benign	
iv. Uterus and		transitional cell papilloma (M F) enithelial	
enididymides were		hyperplasia (M F) polyp (one female) chronic	
not weighed		inflammation (M F) kidneys (enithelial hyperplasia	
v Coagulating		(M F) renal papillary degeneration/necrosis (M F) *	
aland iloum		renal cortical scarring (M E) palvis polyn (one male) $\uparrow$	
5шии, шемт,		renar cortical scarring (wi, r) pervis polyp (one male),	

 Table 2.6.5-1. Summary table of animal studies on long-term toxicity and carcinogenicity

RMS: SE Co-RMS: DE

	F	ſ	ř
Method,	Test substance,	Results	Reference
guideline,	dose levels	- NOAEL/LOAEL	
deviations if any,	duration of	- target tissue/organ	
species, strain,	exposure	- critical effects at the LOAEL (bold text)	
sex, no/group			
lacrimal gland and		renal focal calcification, <u>ureter (epithelial hyperplasia</u>	
seminal vesicle		(M, F), urethra (epithelial hyperplasia (M, F)), adrenals	
were not		(benign phaeochromocytoma M, F), pancreas	
investigated for		(↑pancreatic acinar atrophy (M, F), parathyroid	
histopathology		(epithelial hyperplasia (M), mammary gland	
		$(\downarrow$ mammary acinar development and secretion (F)),	
GLP: No		lungs (arterial calcification (M, F), ovaries (lack of	
		cyclic activity))	
		NOAEL for systemic toxicity (M, F): 4 ppm	
		(corresponds to 0.21 and 0.28 mg/kg bw/day in males	
		and females, respectively)	
		NOAEL for tumour incidence (M, F): 52 ppm	
		(corresponds to 2.82 and 3.65 mg/kg bw/day in males	
		and females, respectively)	
Carcinogenicity	ACN technical	<u>3 ppm:</u>	RAR Vol. 3,
study	(Quinoclamine)	-clinical signs (orange fur staining) (M, F)	B.6.5.2/01
Oral (dietary)	Purity: 98.57%	<u>30 ppm:</u>	Anonymous 24 (1993)
		↑mortality (M, F)	
No guideline	0, 3, 30 or 300	-clinical signs (orange fur staining) (M, F)	New data for the Annex I
claims in study	ppm	-changes in organ weights (frel kidney, M: 14% n.s.)	renewal: No
report	(corresponding to	-histopathological changes in <u>adrenal</u> (adrenal spindle	
	averages of 0,	cell hyperplasia (F), brown athrophy (F)); <u>Stomach</u>	
Mouse	0.38, 3.82 and	(hyperkeratosis and chronic inflammation (F))	
	40.2  mg/kg	200	
CrI:CD-1 (ICR)BR	bw/day in males	$\frac{300 \text{ ppm:}}{100000000000000000000000000000000000$	
50/ /	and 0, 0.44, 4.48	$\uparrow$ mortality (M, F)	
50/sex/group	and 46.4 mg/kg	-clinical signs (orange fur staining) (M, F)	
The study was	bw/day in	$\downarrow$ <b>DW gain</b> (M: 55%, F: 50%)	
the study was	lemales)	-changes in organ weights ([1c] liver ( $\Gamma$ . 2070), [1c]	
compliance with	80 weeks	Address (W. 15% i.s., $1^{\circ}$ , 24% ii.s.), [10] iicart (1),	
OFCD TG 151	ou weeks	-histonathological changes in adrenal (*adrenal	
(adopted 7		spindle cell hyperplasia (M) thrown athrony (F))	
Sentember 2009)		kidney (cortical scarring (M E) hydronenbrosis (M	
Following		F) liver (chronic inflammation (F) brown	
deviations were		nigmentation (F)) sciatic nerve (degeneration (F))	
noted.		spleen (haemosiderosis (F) heart (generalised	
i, the duration of		periarteritis (F), myocardial fibrosis (13 M, 2 F)).	
study was 20		stomach (hyperkeratosis (M, F), epithelial hyperplasia	
months (according		(M), dilation of mucosal glands (M, F)), urinary	
to the guideline the		bladder (epithelial hyperplasia (particularly F)), urether	
duration of the		(dilation (M, F)), lymph nodes (histiocytosis (M, F).	
study will normally		lympho reticular tissues (malignant lymphoma (F))	
be 24 months for			
rodents. Shorter or		NOAEL (M, F): 3 ppm (corresponding to 0.38 and	
longer study		0.44 mg/kg bw/day for males and females,	
durations may be		respectively)	
used but should be			
justified).		LOAEL (M, F): 30 ppm (corresponding to 3.82 and	
ii. cervix,		4.48 mg/kg bw/day in males and females, respectively)	
coagulating gland,			
Hardian gland and		NOAEL for tumour incidence (F): 30 ppm (4.48 mg/kg	
lacrimal gland		bw/day)	
were not included			
in the		NOAEL for tumour incidence (M): 300 ppm (40.2	
		mg/kg bw/day)	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL (bold text)	Reference
histopathological evaluation.			
GLP: Yes			

#### Table 2.6.5-2. Summary table of human data on long-term toxicity and carcinogenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data				

Table 2.6.5-3. Summary table of other studies relevant for long-term toxicity and carcinogenicity

Type of	Test	Relevant information about the	Observations	Reference
study/data	substance	study (as applicable)		
No data				

# 2.6.5.1 Short summary and overall relevance of the provided information on long-term toxicity and carcinogenicity

The data available to assess this endpoint include one combined chronic toxicity/carcinogenicity study in the rat and one carcinogenicity study in the mouse. The studies are thoroughly presented in Vol. 3 to the RAR. The mouse study was conducted in accordance with the OECD Principles of Good Laboratory Practice (1981) but not the rat study. Both studies are however acceptable.

#### Combined chronic toxicity/carcinogenicity study in the rat (RAR Vol. 3, B.6.5.1/01):

In this study, treatment was associated with <u>clinical signs</u> (orange fur staining and reduced incidence of mass bearing) noted in both sexes at 676 ppm (37.6 and 38.3 mg/kg bw/day in males and females, respectively), <u>reduced bodyweight gain</u> noted in females at 676 ppm (carcinogenicity evaluation: 27%; toxicology evaluation: 28%), <u>reduced food consumption</u> noted in both sexes at 676 ppm, <u>changes in haematological parameters</u> (reduced packed blood cell volume, haemoglobin concentration and red blood cell count) noted in both sexes at 676 ppm, <u>changes in biochemical parameters</u> noted at 676 ppm (elevated blood urea nitrogen levels noted in males (n.s) and females (n.s.), reduced calcium noted in males (s.s.) and females (n.s.), reduced inorganic phosphorous noted in males (n.s.) and females (s.s.), reduced lactate dehydrogenase noted in both sexes), <u>findings in urinalysis</u> such as yellow/brown or orange discoloration noted in both sexes in all treated groups and diuretic males noted at

676 ppm, <u>changes in organ weights</u> (increased relative kidney weights noted in males at  $\geq$ 52 ppm ( $\geq$ 2.82 mg/kg bw/day), and in females at 676 ppm; increased relative spleen weights noted in females at 676 ppm; increased relative thymus weight noted in females at 676 ppm; increased relative thymus weight noted in females at 676 ppm; increased relative heart weight noted in females at 676 ppm; increased relative heart weight noted in females at 676 ppm; increased relative adrenal weights noted in females at 676 ppm; increased relative brain weights noted in females at 676 ppm), gross pathology findings in the urinary bladder (orange discoloration) and skin (orange staining) noted in both sexes at 676 ppm, and <u>histopathological changes</u> noted in the urinary bladder (both sexes,  $\geq$ 52 ppm corresponding to 2.82 and 3.65 mg/kg bw/day in males and females, respectively), kidneys (both sexes at  $\geq$ 52 ppm), ureter (both sexes at 676 ppm), parathyroid (males at 676 ppm), mammary gland (females at 676 ppm) and lungs (males at  $\geq$ 52 ppm and females at 676 ppm).

Neoplastic changes were noted in the <u>urinary bladder</u> (benign transitional cell papilloma noted in males at  $\geq$ 52 ppm and in females at 676 ppm) and <u>adrenals</u> (increased incidence of benign phaeochromocytoma noted in both sexes at 676 ppm). The benign transitional cell papilloma noted in one single male at 52 ppm was considered of no clear relevance. No other differences in tumour incidence or type were seen which were considered to be dependent on the dose levels of ACN-technical.

Non-neoplastic changes in the <u>urinary bladder</u> consisted of: epithelial hyperplasia (both sexes at  $\geq$ 52 ppm, corresponding to  $\geq$ 2.82 and  $\geq$ 3.65 mg/kg bw/day in males and females, respectively), polyp noted in one female at 676 ppm (38.3 mg/kg bw/day) and chronic inflammation noted in both sexes at 676 ppm (37.6 and 38.3 mg/kg bw/day in males and females, respectively). Non-neoplastic changes in the <u>kidneys</u> consisted of: epithelial hyperplasia (both sexes at  $\geq$ 52 ppm), renal papillary degeneration/necrosis (both sexes at 676 ppm), increased incidence of renal cortical scarring (both sexes at 676 ppm), pelvis polyp noted in one male at 676 ppm and increased incidence of renal focal calcification (in females at  $\geq$ 52 ppm), and in the <u>parathyroid</u> (males at 676 ppm). Non-neoplastic changes in <u>pancreas</u> consisted of increased incidence of pancreatic acinar atrophy (both sexes at 676 ppm). The histopathological changes in the <u>mammary gland</u> consisted of decreased incidence of mammary acinar development and secretion (females at 676 ppm). Increased incidence of arterial calcification was noted in the <u>lungs</u> (males at  $\geq$ 52 ppm, females at 676 ppm).

NOAEL for systemic toxicity was 4 ppm (corresponding to 0.21 and 0.28 mg/kg bw/day for males and females, respectively) based on reduced bodyweight gain noted in females at 676 ppm (38.3 mg/kg bw/day), changes in haematological parameters noted in both sexes at 676 ppm (37.6 and 38.3 mg/kg bw/day in males and females, respectively), changes in biochemical parameters noted in both sexes at 676 ppm, changes in organ weights (increased kidney weight noted in males at  $\geq$ 52 ppm and in females at 676 ppm; increased thyroid, thymus, heart and adrenals noted in females at 676 ppm), changes in urinalysis noted in both sexes at  $\geq$ 52 ppm (At 52 ppm and 676 ppm: yellow/brown to orange discoloration; At 676 ppm: diuretic males), macroscopic changes noted in both

sexes at 676 ppm (discoloration in urinary bladder and skin) and histopathological changes noted in both sexes at  $\geq$ 52 ppm.

NOAEL for tumour incidence was 52 ppm (corresponding to 2.82 and 3.65 mg/kg bw/day in males and females, respectively) based on benign transitional cell papillomas in urinary bladder and increased incidence of benign phaeochromocytoma in adrenals noted in both sexes at 676 ppm.

Relevance of neoplastic changes- benign transitional cell papilloma in urinary bladder:

Treatment related neoplastic changes in the carcinogenicity study were confined to the presence of benign transitional cell papillomas in the urinary bladder of 4/47 males and 6/50 females in high dose group (676 ppm) at week 104 (Table B.6.5.1-1). These benign tumours were considered by the study author not to have been the cause of death in any animal but a transitional cell papilloma together with renal papillary lesions were considered to be the predominant pathology in one high dose female which was killed in extremis. The tumours were characterised by discrete exophytic epithelial masses with branching papillary processes supported by a fibrovascular core. The majority of these tumours appeared to have developed from a base of hyperplastic epithelium showing changes similar to the non-neoplastic epithelial hyperplasia seen in both high and intermediate dose group animals according to study author (Table B.6.5.1-3). No epithelial cellular atypia was seen and there was no neoplastic invasion of subepithelial connective tissues or muscle. The tumour in one female (killed in extremis) diagnosed as a probable transitional cell papilloma was described at necropsy as a pedunculated mass within the bladder and at microscopy was seen to be a large necrotic mass in the bladder lumen with no evidence of neoplastic invasion of the bladder wall.

Transitional cell papillomas in association with epithelial hyperplasia in the urinary bladder were also found in the toxicity study at week 104 (one male and two females from the high dose groups, and a single intermediate dose male) (Table B.6.5.1-2). The significance of the occurrence of a single tumour in one male intermediate dose animal is not clear. Epithelial hyperplasia noted in the treated animals was characterised by a generalised increase in the number of layers of cells in the urinary epithelium. The normal epithelium consisted of two to three layers of cells, minimal hyperplasia by five to eight layers of cells and marked hyperplasia by more than eight layers of cells. In several animals two degrees of hyperplasia were seen with focal area of moderate hyperplasia associated with diffuse minimal hyperplasia. Squamous metaplasia of the urinary epithelium was associated with epithelial hyperplasia in two high dose females. Epithelial haemorrhage was noted in two male and one female high dose animals. Acute inflammation was seen in association with a bladder tumour in an intermediate dose male (Table B.6.5.1-4).

Table 2.6.5.1-1: Transitional cell papilloma of the urinary bladder (carcinogenicity evaluation)

	Males			Females				
	0	4	52	676	0	4	52	676
Total: number examined	50	49	47	47	49	48	49	50
Transitional cell papilloma	0	0	0	4	0	0	0	6

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Terminal kill: number examined	27	27	20	30	26	29	30	38
Transitional cell papilloma	0	0	0	3	0	0	0	5
Killed in extremis: number examined	17	18	21	6	19	16	19	10
Transitional cell papilloma	0	0	0	0	0	0	0	1
Died: number examined	6	4	6	11	4	3	0	2
Transitional cell papilloma	0	0	0	1	0	0	0	0

#### Table 2.6.5.1-2: Neoplastic pathology Terminal (104 week): Urinary bladder (toxicity evaluation)

	Males	Males			Females			
	0	4	52	676	0	4	52	676
Total: number examined	9	10	9	5	11	9	10	15
Transitional cell papilloma	0	0	1	1	0	0	0	2

# Table 2.6.5.1-3: Non-neoplastic pathology-urinary bladder (carcinogenicity evaluation)

	Males				Femal	es		
	0	4	52	676	0	4	52	676
Total: number examined	50	49	47	47	49	48	49	50
Epithelial hyperplasia	3	2	5	41	1	1	6	46
Squamous metaplasia	0	0	0	0	0	0	0	3
Polyp	0	0	0	0	0	0	0	1
Cystitis/inflammation	1	2	1	3	0	0	0	2
Haemorrhage	0	0	0	1	0	0	0	2
Terminal kill: number	27	27	20	30	26	29	30	38
examined								
Epithelial hyperplasia	0	0	0	28	1	1	0	35
Squamous metaplasia	0	0	0	0	0	0	0	2
Polyp	0	0	0	0	0	0	0	1
Cystitis/inflammation	0	0	0	0	0	0	0	2
Haemorrhage	0	0	0	0	0	0	0	2
Killed in extremis: number	17	18	21	6	19	16	19	10
examined								
Epithelial hyperplasia	2	2	4	5	0	0	6	9
Squamous metaplasia	0	0	0	0	0	0	0	1
Polyp	0	0	0	0	0	0	0	0
Cystitis/inflammation	0	2	0	1	0	0	0	0
Haemorrhage	0	0	0	0	0	0	0	0
Died: number examined	6	4	6	11	4	3	0	2
Epithelial hyperplasia	1	0	1	8	0	0	0	2
Squamous metaplasia	0	0	0	0	0	0	0	0
Polyp	0	0	0	0	0	0	0	0
Cystitis/inflammation	1	0	1	2	0	0	0	0
Haemorrhage	0	0	0	1	0	0	0	0

# Table 2.6.5.1-4: Non-neoplastic pathology-urinary bladder (toxicity evaluation week 104)

	Males				Females			
	0	4	52	676	0	4	52	676
Total: number examined	9	10	9	5	11	9	10	15
Epithelial hyperplasia- total	0	0	2	5	1	0	0	15
Squamous metaplasia	0	0	0	0	0	0	0	2
Haemorrhage	0	0	0	2	0	0	0	1
Cystitis/acute inflammation	0	0	1	0	0	0	0	0
Chronic inflammation	0	0	1	0	1	0	1	0
Eosinophilic plug	0	0	1	0	0	0	0	0

# RMS conclusion:

The findings of benign cell papillomas in urinary bladder shows that when fed at a dose level of 676 ppm the test article or its metabolites can cause the development of benign epithelial tumours of the urinary bladder. There is however no evidence in this study that the feeding of the test compound at dose levels of up to 676 ppm for a period of two years induces the development of malignant tumours in the urinary bladder.

#### Relevance of neoplastic changes- benign phaeochromocytoma in adrenal:

There was an apparent increase in the incidence of benign phaeochromocytomas of the adrenal medulla in high dose animals noted in the carcinogenicity study (Table B.6.5.1-5). Although the incidences were outside the ranges for benign phaeochromocytoma from historical control data in study report (Table B.6.5.1-6), they were considered not to be of biological significance by the study author, and were shown not to be of clear statistical significance. No increased incidence of benign phaeochromocytomas of the adrenal medulla was noted in the toxicity study.

· · · · · ·	Males		,	0 1	Fema	les		
	0	4	52	676	0	4	52	676
Total: number examined	50	24	28	47	50	29	27	50
Benign phaeochromocytoma	8	4	2	14	1	0	0	4
Malign phaeochromocytoma	2	0	0	1	0	0	0	0
Medullary hyperplasia	7	4	3	7	3	3	0	6
Terminal kill: number examined	27	2	0	30	26	8	7	38
Benign phaeochromocytoma	5	1	0	10	1	0	0	4
Malign phaeochromocytoma	2	0	0	1	0	0	0	0
Medullary hyperplasia	4	0	0	5	2	0	0	4
Killed in extremis: number examined	17	18	21	6	19	16	19	10
Benign phaeochromocytoma	2	1	2	2	0	0	0	0
Malign phaeochromocytoma	0	0	0	0	0	0	0	0
Medullary hyperplasia	3	4	2	2	1	2	0	2
Died: number examined	6	4	7	11	5	5	1	2
Benign phaeochromocytoma	1	2	0	2	0	0	0	0
Malign phaeochromocytoma	0	0	0	0	0	0	0	0
Medullary hyperplasia	0	0	1	0	0	1	0	0

Table 2.6.5.1-5: Phaeochromocytoma of the adrenal medulla (carcinogenicity evaluation)

The trend was statistically significant (p<0.05) for combined sexes

#### Table 2.6.5.1-6: Historical control data (in study report)

Tumour: background incidence data from carcinogenicity studies conducted at the laboratory in question											
Total number of animals examined: 349											
	Cumulative incidence	Cumulative percentage	Individual percentage								
		incidence	incidence range								
Males											
Benign phaeochromocytoma	42	12.0	6.0-16.0								
Malign phaeochromocytoma	1	0.3	0.0-2.0								
Females											
Benign phaeochromocytoma	8	2.3	0.0-4.0								
Malign phaeochormocytoma	1	0.3	0.0-2.0								

RMS conclusion:

Medullary hyperplasia

Increased incidence of benign phaeochromocytomas of the adrenal medulla in high dose animals was noted in the carcinogenicity study. The trend was statistically significant (p<0.05) for combined sexes. No increased incidence of benign phaeochromocytoma was noted in the toxicity study but it could be noted that few animals were examined at interim sacrifice time. The incidence of malignant phaeochromocytoma in adrenals was not increased in the study.

#### Carcinogenicity study in the mouse (RAR Vol. 3, B.6.5.2-01):

In this study, treatment was associated with clinical signs (orange fur staining) noted in both sexes at  $\geq$ 3 ppm, increased mortality noted in both sexes at  $\geq$ 30 ppm, reduced bodyweight gain (33% in males, 30% in females) noted at  $\geq$ 300 ppm, changes in organ weight noted at  $\geq$ 30 ppm (increased relative liver weight noted in females at 300 ppm, increased relative kidney weights (n.s.) noted in males at  $\geq$ 30 ppm and in females at 300 ppm, increased relative heart and brain weights noted in females at 300 ppm), histopathological changes (At 300 ppm: increased incidence of malignant lymphoma noted in females, increased incidence of adrenal spindle cell hyperplasia noted in males, increased incidence of adrenal atrophy noted in females, kidney cortical scarring and hydronephrosis noted in both sexes, hepatic chronic inflammation and brown pigmentation noted in females, sciatic nerve degeneration noted in females, spleenic haemosiderosis noted in females, generalised periarteritis in females, myocardial fibrosis in particularly in males, hyperkeratosis in the stomach noted in both sexes, epithelial hyperplasia of the urinary bladder (particularly in females), dilatation of the ureters in both sexes and histiocytosis of lymph nodes in both sexes; At 30 ppm: adrenal spindle cell hyperplasia and adrenal atrophy noted in females, and hyperkeratosis and chronic inflammation in the stomach in females).

The mortality in the study was exceptionally low, especially in controls. Only at the highest dose level (300 ppm) did mortality approach the levels expected in comparison to historical control data (-50%) (Table below)

ACN technical (ppm)	Male		Female	
	Died	Killed in extremis	Died	Killed in extremis
0	6/50 (12%)	2/50 (4%)	5/50 (10%)	4/50 (8%)
3	12/50 (24%)	6/50 (12%)	7/50 (14%)	5/50 (10%)
30	15/50 (30%)	4/50 (8%)	11/50 (22%)	3/50 (6%)
300	17/50 (34%)	8/50 (16%)	19/50 (38%)	2/50 (4%)

Mortalities (%) divided by died and killed in extremis by the end of week 80

NOAEL was 3 ppm (0.38 and 0.44 mg/kg bw/day for males and females, respectively) based on increased mortality noted in both sexes at  $\geq$ 30 ppm, reduced bodyweight gain (33% in males, 30% in females) noted at  $\geq$ 300 ppm, increased relative liver weight noted in females at 300 ppm, increased relative kidney weights noted in males at  $\geq$ 30 ppm and in females at 300 ppm and histopathological changes noted in the adrenal and stomach at  $\geq$ 30 ppm and in the kidney, urether, urinary bladder, liver, sciatic nerve, spleen, heart and lymph nodes noted at 300 ppm, and malignant lymphoma noted in females at 300 ppm.

#### Discussion- tumour incidence:

There were weakly statistically significant (p<0.05) positive trends for adrenal spindle cell tumour or hyperplasia (in fact virtually all hyperplasia in males but not in females), malignant lymphoma in females, but not males and histiocytic sarcoma (but only when both sexes were combined). Tumours identified in study are presented in Table 2.6.5.1-7.

Site	Tumour	Males				Females			
		Control	3	30	300	Control	3	30	300
			ppm	ppm	ppm		ppm	ppm	ppm
Adenoma cortical	Cortical hyperplasia	3	1	0	2	0	0	0	0
Adrenal cortex	Benign tumour	3	0	1	2	0	0	1	0
	Tumour or hyperplasia	5	0	1	4	0	0	1	0
Adrenal spindle cell	Hyperplasia	11	3	4	18*	33	36	41*	30
	Spindle cell adenoma	0	0	0	0	1	0	0	0
Adrenal medulla	Hyperplasia	1	1	0	2	0	0	0	0
Harderian gland	Adenoma	3	1	1	0	1	0	0	0
Liver hepatocellular	Malignant tumour	4	3	4	4	1	0	0	0
	Haemangiosarcoma	0	1	0	0	0	0	0	0
	Benign tumour	9	7	7	5	0	1	0	0
	Adenoma	5	8	6	5	0	0	0	0
	Hyperplasia	2	2	0	2	0	1	0	0
Lung pulmonary	Carcinoma	7	4	7	1	2	2	1	1
	Haemangiosarcoma	0	0	0	1	0	1	0	0
	Hyperplasia	4	5	2	7	8	3	5	3
	Adenoma	10	11	7	8	1	7	2	2
Pancreas islet cell	Hyperplasia	3	1	0	0	2	0	0	0
Pituitary	Tumour or hyperplasia	0	0	1	0	1	0	0	1
	Benign tumour	0	0	1	0	0	0	0	1
Testis interstitial-cell	Cell adenoma	2	0	0	3	-	-	-	-
	Tumour or hyperplasia	5	0	1	2	-	-	-	-
Thyroid gland	Follicular adenoma	0	3	1	2	1	0	1	0
	Follicular hyperplasia	0	1	0	0	1	0	0	0
Skin/subcutaneous tissue	Lipoma	1	0	0	0	2	1	1	1
	Fibrosarcoma	0	1	0	0	5	4	2	8
Skin/subcutis epithelial	Fibrosarcoma	3	0	1	0	0	2	0	0
	Carcinoma	0	0	1	0	0	0	0	0
	Epidermal hyperplasia	18	14	18	15	0	0	0	0
Smooth muscle	Benign or malignant	0	0	0	1	2	1	2	1
	tumour								
Fibrous tissue	Malignant tumour	3	1	1	0	0	1	1	0
Skin epidermal	Hyperplasia	0	5	2	9	6	2	21	15
	Fibrosarcoma	3	0	2	0	0	0	0	0
	Squamous carcinoma	0	0	0	1	0	1	0	0
	Squamous papilloma								
Kidneys	Osseus metaplasia	0	0	0	1	0	0	0	0
Lympho reticular tissues	Malignant lymphoma	1	2	3	0	3	11	7	12
	Histiocytic sarcoma	0	0	0	1	0	1	1	2

# Table 2.6.5.1-7: Tumours identified

\*Significance at p<0.05, two-tailed probability values based on the chi squared test

Discussion- Malignant lymphoma:

Malignant lymphoma were seen in 1 male and 3 females in the control. In females there was a marginally significant (p<0.05) positive trend due mainly to a higher incidence at 300 ppm (12 cases) (Table 2.6.5.1-7) than in the controls (3 cases). The dose-response relationship was not smooth and no evidence of an effect was seen in males. In the study report, historical control data for Crl:CD-1(ICR)BR (VAF PLUS) mice are reported showing that the occurrence of malignant lymphoma in background data of females ranged from 2 to 11 cases (Table 2.6.5.1-9). In document "Reporting Table No. 2(8) (2007)" applicant has presented additional historical background data for CD-1 mouse for the laboratory in question (studies conducted between years 1991 to 1994), showing that the occurrence of malignant lymphoma in females ranged from 0-38%. According to the applicant the trend in the current study seems likely to be due to chance finding. It is stated by the study author, that a possible explanation for the increased variability might be a "cage effect". The meaning of "cage effect" was however not specified by the study author, and a substance related effect could not be excluded.

<u>Comment by Co-RMS</u>: It is proposed that the positive trend is not ignored and a substance related effect cannot be excluded. Therefore, the increased trend for malignant lymphoma in mice supports the proposed classification as carcinogenic in Cat. 2 (H351).

Table 2.6.5.1-8: Historical control data-lympho reticular tissues. Tumour incidence in untreated Crl:CD-1(ICR)BR (VAF PLUS) male mice from carcinogenicity studies (in study report)

Number examined	50	50	50	50	50*	50	50	50*
Study duration in weeks	80	80	80	80	80	96	80	80
Malignant lymphoma	3	1	3	0	0	0	2	1
Monocytic leukaemia	1	0	0	0	0	0	0	0
Histiocytic sarcoma	0	0	1	0	1	0	0	0

\* All were dietary and group housed, except those marked \* which were singly housed, dermal studies

Table 2.6.5.1-9: Historical control data-lympho reticular tissues. Tumour incidence in untreated Crl:CD-1(ICR)BR (VAF
PLUS) female mice from carcinogenicity studies (in study report)

Number examined	50	50	50	50	50	50*	50	50	50*
Study duration in weeks	80	80	80	80	80	96	80	80	80
Malignant lymphoma	6	3	2	3	2	8	3	7	11
Monocytic leukaemia	1	1	1	1	0	0	0	0	0
Histiocytic sarcoma	0	0	3	3	1	6	3	2	3

\* All were dietary and group housed, except those marked \* which were singly housed, dermal studies

Table 2.6.5.1-10: Historical control	l data-haemopoietic tiss	ie. Neoplastic historical	control information	in male CD-1
mouse for the laboratory in question	n (1991-1994) (data prov	ided by applicant after j	preparation of DAR)	

										_			
Study No.*	1	3	4	5	6	2	7	8	9	10	11		
End Date	1991	1992	1992	1992	1992	1993	1994	1994	1994	1994	1994		
Animals/cage	5	1	1	5	5	4	5	5	5	5	5		
No.	50	60	60	50	50	50	55	55	25	25	50	Total	Range of
examined												530	percentages
M-histiocytic s	sarcoma												
Incidence	0	2	1	0	0	0	0	2	0	0	0	5	
Percentage	0.0%	3.3%	1.7%	0.0%	0.0%	0.0%	0.0%	3.6%	0.0%	0.0%	0.0%	0.9%	0.0-3.6%
M-lymphoma													
Incidence	1	2	3	3	3	1	3	2	1	0	7	26	
Percentage	2.0%	3.3%	5.0%	6.0%	6.0%	2.0%	5.5%	3.6%	4.0%	0.0%	14.0%	4.9%	0.0-14.0%
								 			-		

\* Dose route: Dietary (study no. 1, 2, 6 and 11), gavage (study no. 3, 4, 7, 8, 9, 10), subcut (study no. 5)

mouse for the	140014	cory mic	lacouou	(1//1 1)	· · · · (uu	m provin	aca by	appnea	ne areer	prepara	cion or i		
Study No.*	1	3	4	5	6	2	7	8	9	10	11		
End Date	1991	1992	1992	1992	1992	1993	1994	1994	1994	1994	1994		
Animals/cag	5	1	1	5	5	4	5	5	5	5	5		
e													
No.	50	60	60	50	50	50	55	55	25	25	50	Total	Range of
examined												530	percentage
													S
M-histiocytic	sarcoma	1											
Incidence	0	3	3	2	0	1	1	0	1	0	4	15	
Percentage	0.0	5.0%	5.0%	4.0%	0.0%	2.0%	1.8	0.0	4.0%	0.0%	8.0%	2.8%	0.0-8.0%
	%						%	%					
M-lymphoma													
Incidence	3	6	6	12	6	19	4	0	3	3	9	71	
Percentage	6.0	10.0	10.0	24.0	12.0	38.0	7.3	0.0	12.0	12.0	18.0	13.4	0.0-38.0%
_	%	%	%	%	%	%	%	%	%	%	%	%	

Table 2.6.5.1-11: Historical control data-haemopoietic tissue. Neoplastic historical control information in female CD-1 mouse for the laboratory in question (1991-1994) (data provided by applicant after preparation of DAR)

\* Dose route: Dietary (study no. 1, 2, 6 and 11), gavage (study no. 3, 4, 7, 8, 9, 10), subcut (study no. 5)

#### Discussion-Histiocytic sarcoma:

No occurrence of histiocytic sarcoma was reported for the control. When treatment results for the sexes were combined, the trend, with 3 cases at 300 ppm (Table 2.6.5.1-7) was marginally significantly positive (p<0.05). The histiocytic sarcoma incidence was within background for both historical control data sets. In the study report, historical control data for Cr1:CD-1(ICR)BR (VAF PLUS) mice are reported showing that the occurrence of histiocytic sarcoma in background data of mice ranges from 0 to 1 case in males, and 0-6 cases in females (Table 2.6.5.1-9 to 10). In document "Reporting Table No. 2(8) (2007)" applicant has presented additional historical background data for CD-1 mouse for the laboratory in question (studies conducted between years 1991 to 1994), showing that the occurrence of histiocytic sarcoma in background data suggests this is a chance finding due to an unusually low incidence on the controls in this study.

#### Discussion- Adrenal cortex/adrenal spindle cells (with and without control):

A spindle-cell adenoma was seen in one female (control), with spindle-cell hyperplasia (usually graded as minimal) seen in a further 11 males (control) and 33 female (control) (Table 2.6.5.1-7). In females, no dose-relationship was seen, but incidence of spindle-cell hyperplasia at 30 ppm was marginally significantly elevated (p<0.05) compared to the controls. In males, there was a significant increase (p<0.05) at 300 ppm. Cortical adenomas were seen in 6 males and 1 female (Table 2.6.5.1-7), however, no increased incidence was noted in treated groups compared to the control group, thus this incidence was unrelated to treatment. As a conclusion, there was no evidence of tumour formation in the adrenal.

Comment: No historical control data are available for adrenal spindle cell hyperplasia.

#### RMS conclusion:

The incidence of 3 histiocytic sarcoma at 300 ppm (showing a statistical significant positive trend but only when both sexes were combined) was within background for both historical control data sets. The occurrence of histiocytic sarcoma in background data suggests this is a chance finding due to an unusually low incidence on the controls in this study.

The adrenal spindle cell hyperplasia was significantly elevated for males at the top dose and at 30 ppm in females, thus there were no clear dose response relationship. Furthermore, there were no significant increases in benign or malign adrenal tumours.

The incidence of malignant lymphoma in females of the high dose group showed a significantly increased trend and was slightly outside historical control data in study report. Althought the incidence of malignant lymphoma did not show a smooth dose-response pattern, a treatment related effect could not be excluded.

# 2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
Rat	Urinary bladder benign transitional cell papilloma	Yes (two tumour types in one species)	No	No	Both sexes	No	Oral (dietary)	No data
Rat	Adrenal benign phaeochomocytoma	Yes (two tumour types in one species)	No	No	Both sexes	No	Oral (dietary)	No data

 Table 2.6.5.2-1. Compilation of factors to be taken into consideration in the hazard assessment

According to Regulation 1272/2008 (CLP) substances are classified for carcinogenicity in Category 1 (known or presumed human carcinogens) on the basis of epidemiological and/or animal data. Category 1 is subcategorised into 1A if the substance is "known to have carcinogenic potential for humans, classification is largely based on human evidence" and 1B if "presumed to have carcinogenic potential for humans classification is largely based on animal evidence."

As there is no human data available for quinoclamine that may be relevant for carcinogenicity, criteria for category 1A are not fulfilled.

For classification in category 1B evidence may be derived from "[...] 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."

Sufficient evidence from animal studies is explained as "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. [...]"

Quinoclamine does not fulfil these criteria. Benign transitional cell papillomas in urinary bladder and phaeochromocytoma in adrenals were only found in one species (rat) and in one study. The incidence of malignant lymphoma was noted in one species only (mouse) and was slightly outside the historical control data in study report but was within historical control data submitted by the applicant. The effect showed no smooth dose response and was difficult to rule out.

The effects noted in the rat and mouse were not considered of a convincing evidence for a classification in category 1B.

The placing of 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 (2) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies."

Limited evidence from animal studies is explained as "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 organs"

The significance of tumours observed in the chronic toxicity/carcinogenicity study in the rat, i.e. benign transitional cell papillomas in urinary bladder and phaeochromocytoma in adrenals, and the malignant lymphoma noted in female mice is discussed below based on considerations included in the CLP guidance:

(a) tumour type and background incidence;

# Tumour type:

Benign transitional cell papillomas in urinary bladder in the Crl:CD(SD)BR rat Benign phaeochromocytoma in adrenals in the Crl:CD(SD)BR rat Malignant lymphoma in female mouse (Crl:CD-1 (ICR) BR strain)

Background incidence:

Historical control data for benign transitional cell papilloma and benign phaeochromocytoma in adrenals in the rat are available in study report (time period for studies not specified) (Table 2.6.5.2-2)

phaeoem omocy toma in auten	ans (rat)		
Tumour: background incidenc	e data from carcinogenicity s	studies conducted at the laborato	ry in question
Total number of animals exam	nined: 349		
	Cumulative incidence	Cumulative percentage	Individual percentage
		incidence	incidence range
Males			
Benign transitional cell	1	0.3	0.0-2.0
papillomas in urinary			
bladder			
Benign phaeochromocytoma	42	12.0	6.0-16.0
in adrenals			
Malign phaeochromocytoma	1	0.3	0.0-2.0
in adrenals			
Females			
Benign transitional cell	_1	_1	_1
papillomas in urinary			
bladder			
Benign phaeochromocytoma	8	2.3	0.0-4.0
in adrenals			
Malign phaeochromocytoma	1	0.3	0.0-2.0
in adrenals			
1			

# Table 2.6.5.2-2: Historical control data for benign transitional cell papilloma in urinary bladder and benign phaeochromocytoma in adrenals (rat)

<sup>1</sup>No data

The incidence of benign transitional cell papillomas in urinary bladder noted in the rat was 4/47 (9%) in males and 6/50 (12%) in females. The frequencies observed in the study for males are outside of the background incidence of 2.0 (Table 2.6.5.2-2). Thus, the tumour can be considered to result from treatment with quinoclamine. No historical control data for this tumour type was available for females.

The incidence of benign phaeochromocytoma in adrenals noted in the rat was 14/47 (30%) in males and 4/50 (8%) in females. The frequencies observed in the study for males and females are outside of the background incidence of 16% and 4% for males and females, respectively (Table 2.6.5.2-2). Thus, the tumour can be considered to result from treatment with quinclamine.

*Historical control data for malignant lymphoma in the mouse (Table 2.6.5.2-3)* 

Table 2.6.5.2-3: Historical control data-lympho	reticular	tissues. 7	Fumour i	incidence	e in untreat	ted Crl:C	D-1(ICF	R)BR (VAF
PLUS) male mice from carcinogenicity studies	(in study	report, t	ime spar	ns for stu	dies not sp	ecified)		

Number examined	50	50	50	50	50*	50	50	50*
Study duration in weeks	80	80	80	80	80	96	80	80
Malignant lymphoma	3	1	3	0	0	0	2	1
Monocytic leukaemia	1	0	0	0	0	0	0	0
Histiocytic sarcoma	0	0	1	0	1	0	0	0

Table 2.6.5.2-4: Historical control data-lympho reticular tissues. Tumour incidence in untreated Crl:CD-1(ICR)BR (VAF
PLUS) female mice from carcinogenicity studies (in study report, time spans for studies not specified)

· · · · · · · · · · · · · · · · · · ·									
Number examined	50	50	50	50	50	50*	50	50	50*
Study duration in weeks	80	80	80	80	80	96	80	80	80
Malignant lymphoma	6	3	2	3	2	8	3	7	11
Monocytic leukaemia	1	1	1	1	0	0	0	0	0
Histiocytic sarcoma	0	0	3	3	1	6	3	2	3

for the laborat	tor the laboratory in question (1991-1994) (data provided by applicant after preparation of DAR)													
Study No.*	1	3	4	5	6	2	7		8	9	10	11		
End Date	1991	1992	1992	1992	1992	1993	1994		1994	1994	1994	1994		
Animals/cage	5	1	1	5	5	4	5		5	5	5	5		
No.	50	60	60	50	50	50	55		55	25	25	50	Total	Range of
examined													530	percentages
M-histiocytic sarcoma														
Incidence	0	2	1	0	0	0	0		2	0	0	0	5	
Percentage	0.0%	3.3%	1.7%	0.0%	0.0%	0.0%	0.0%		3.6%	0.0%	0.0%	0.0%	0.9%	0.0-3.6%
M-lymphoma														
Incidence	1	2	3	3	3	1	3		2	1	0	7	26	
Percentage	2.0%	3.3%	5.0%	6.0%	6.0%	2.0%	5.5%		3.6%	4.0%	0.0%	14.0%	4.9%	0.0-14.0%

Table 2.6.5.2-5: Historical control data-haemopoietic tissue. Neoplastic historical control information in male CD-1 mouse for the laboratory in question (1991-1994) (data provided by applicant after preparation of DAR)

 Table 2.6.5.2-6: Historical control data-haemopoietic tissue. Neoplastic historical control information in female CD-1

 mouse for the laboratory in question (1991-1994) (data provided by applicant after preparation of DAR)

Study No.*	1	3	4	5	6	2	7	8	9	10	11		
End Date	199	1992	1992	1992	1992	1993	1994	1994	1994	1994	1994		
	1	(Gavag	(Gavag	(Subc	(Die	((die	(Gavag	(Gavag	(Gavag	(Gavag	(Die		
	(Die	e)	e)	ut)	t)	t)	e)	e)	e)	e)	t)		
	t)												
Animals/c age	5	1	1	5	5	4	5	5	5	5	5		
No.	50	60	60	50	50	50	55	55	25	25	50	Tota	Range of
examined												1	percenta
												530	ges
M-histiocyt	ic sarco	ma											
Incidence	0	3	3	2	0	1	1	0	1	0	4	15	
Percentag	0.0	5.0%	5.0%	4.0%	0.0	2.0	1.8%	0.0%	4.0%	0.0%	8.0	2.8	0.0-8.0%
e	%				%	%					%	%	
M-lymphoma													
Incidence	3	6	6	12	6	19	4	0	3	3	9	71	
Percentag	6.0	10.0%	10.0%	24.0%	12.0	38.0	7.3%	0.0%	12.0%	12.0%	18.0	13.4	0.0-
e	%				%	%					%	%	38.0%

The incidence of malignant lymphoma noted in the female mouse was 12/50 (24%). The frequencies were slightly outside of the historical control data in the study report of 11/50 (22%) but within historical control data provided by the applicant (up to 38%) (Table 2.6.5.2-3 to 6). Historical control data indicate high variability.

(b) multi-site responses;

Increased incidence of tumours at multiple sites were noted in the rat (benign transitional cell papillomas in urinary bladder and benign phaeochromocytoma in adrenals). In the mouse one site reponse was noted (malignant lymphoma in females)

(c) progression of lesions to malignancy;

Both types of tumour noted in the rat are considered benign. The type of tumour noted in the mouse (malignant lymphoma) is malign

# Urinary bladder:

The benign transitional cell papillomas in urinary bladder in rats were characterised by discrete exophytic epithelial masses with branching papillary processes supported by a fibrovascular core. The majority of these tumours appeared to have developed from a base of hyperplastic epitheliau showing changes similar to the non-neoplastic epithelial hyperplasia seen in both high and intermediate dose group animals. No epithelial cellular atypia was noted and there was no neoplastic invasion of subepithelial connective tissues or muscle. Thus, a progression into malignancy was not observed.

# Adrenals:

The incidence of malignant phaeochromocytoma in adrenals in rats was not increased in the study. Thus, a progression into malignancy was not observed.

(d) reduced tumour latency;

# Urinary bladder:

The incidence of benign transitional cell papillomas in urinary bladder was noted in rats of both sexes at terminal sacrifice (Week 104). The tumours were not noted in the toxicology evaluation at interim kills (Weeks 26, 52, 78). Thus, there is no indication for reduced tumour latency.

# Adrenals:

The incidence of benign phaeochromocytoma in adrenals in the rat was noted in the carcinogenicity study only. No increased incidence of benign phaeochromocytoma in adrenals was noted in the toxicology study at interim sacrifice (Weeks 26, 52, 78, 104). Thus, there is no indication for reduced tumour latency.

# Lympho reticular tissues:

The incidence of malignant lymphoma in female mice was investigated at study termination (80 weeks).

(e) whether responses are in single or both sexes;

Benign transitional cell papillomas in urinary bladder and benign phaeochromocytoma in adrenals occurred in rats in both sexes. Malignant lymphoma occurred in mice in one sex (females).

(f) whether responses are in a single species or several species;

Benign transitional cell papillomas in urinary bladder and benign phaeochromocytoma in adrenals were observed in rats only. Malignant lymphoma was observed in the mice only. (g) structural similarity to a substance(s) for which there is good evidence of carcinogenicity;

No information available.

(h) routes of exposure;

Information restricted to studies performed using oral administration (via diet).

(i) comparison of absorption, distribution, metabolism and excretion between test animals and humans;

No information on human toxicokinetics available.

(j) the possibility of a confounding effect of excessive toxicity at test doses;

There was no adverse effect on mortality in the rat study. A slightly improved survival was recorded for female rats treated at 676 ppm (Table 2.6.5.2-3). In the mouse study the survival was adversely affected at 30 and 300 ppm (Table 2.6.5.2-4)

Table 2.0.5.2-5: Wortanties in the carcinogenicity (1-4) and toxicology (5-8) groups after 104 weeks [%]									
ACN (ppm)	Male		Female						
	Group 1-4	Group 5-8	Group 1-4	Group 5-8					
0	44	24	48	22					
4	46	26	42	22					
52	60	34	40	24					
676	40	36	24	10					

Table 2.6.5.2-3: Mortalities in the carcinogenicity (1-4) and toxicology (5-8) groups after 104 weeks [%]

Table B.6.5.2/01-01: Mortalities	(%) divided by died and killed in extremis	by the end of week 80

ACN technical (ppm)		Male	Female			
	Died	Killed in extremis	Died	Killed in extremis		
0	6/50 (12%)	2/50 (4%)	5/50 (10%)	4/50 (8%)		
3	12/50 (24%)	6/50 (12%)	7/50 (14%)	5/50 (10%)		
30	15/50 (30%)	4/50 (8%)	11/50 (22%)	3/50 (6%)		
300	17/50 (34%)	8/50 (16%)	19/50 (38%)	2/50 (4%)		

(k) mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity.

No data available.

#### **RMS conclusion:**

Quinoclamine induces benign tumours at multiple sites in Crl:CD(SD)BR rats of both sexes. The type of tumours consisted of benign transitional cell papillomas in urinary bladder and benign phaeochromocytoma in adrenals. In addition, malignant lymphoma was noted in female mice of the Crl: CD-1 (ICR) BR strain but not in males.

The incidences of the tumours noted in the rat (benign transitional cell papillomas in urinary bladder and benign phaeochromocytoma in adrenals) were clearly outside the historical control data, while the indicidence of the tumour noted in the mouse (malignant lymphoma) was just slightly outside the historical control data for the study report.

For the adrenal pheochromocytoma, high spontaneous tumour incidences are reported in male F344 rats and Sprague-Dawley rats (Regulation 1272/2008 (CLP) Part 3, section 3.6.2.3.2). However, although a high spontaneous tumour incidence is reported for some strain of rats, an effect caused by quinoclamine in Crl:CD(SD)BR rats could not be excluded. The incidence in the study was clearly above the historical control data.

With regard to the malignant lymphoma in the mouse, this tumour was noted in one species only and in one sex (females). The incidence (24%) was slightly above the historical control data for the study report (22%) but within historical control data by the applicant (0-38%). Thus, the historical control data showed high variability. However, the effect showed a statistically significant trend, which could not be dismissed, also taking into consideration that the control group in the study takes precedence over historical control data. On the other hand the tumour in the mouse was not a multiple response.

RMS proposes a classification of quinoclamine as carcinogenic in category 2 based on benign tumours (benign transitional cell papillomas in urinary bladder and benign phaeochromocytoma in adrenals) noted in the rat and malignant lymphoma noted in the mouse. The incidence of malignant lymphoma noted in the mouse was not considered of a convincing evidence for a classification in category 1B (no smooth dose response was shown, historical control data showed high variability, no multiple response).

# 2.6.5.3 Conclusion on classification and labelling for carcinogenicity

Classification of quinoclamine as carcinogenic in Category 2 (H351 "Suspected human carcinogens") is proposed.

# 2.6.6 Summary of reproductive toxicity

# 2.6.6.1 Adverse effects on sexual function and fertility – generational studies

Table 2.6.6.1-1. Summary	y table of animal studies or	n adverse effects on se	xual function and fertility	- generational studies
	J			<b>C ·</b> · · · · · · · · · · · · · · · · ·

Method,	Test substance, dose	Results	Reference
deviations if	exposure	fertility, parents)	
any, species,	1	- target tissue/organ	
strain, sex,		- critical effects at the LOAEL (bold text)	
no/group	K 1616	1 ppm;	DAD Vol 3
reproduction	(Ouinoclamine)	Parental:	B.6.6.1/01
study	((	-clinical signs (hunched posture F0/F1)	
2	Purity: 98.5%	↓ bw (P1 M: 3%: P2 M: 7%: P2 F 4%)	Anonymous 19 (1975)
In-house method		$  h_{m} = i \pi (\mathbf{P}   \mathbf{M}, 40) - \mathbf{P}   \mathbf{M}, 110 - \mathbf{P}   \mathbf{F}, 40) \rangle$	
Det	0, 1, 25, 500 ppm	↓ Dw gain (P1 M: 4%, P2 M: 11%; P2 F: 4%)	Report No.: 854-111
Nai	F0.0 0.07 1.6 30.9	Offspring:	New data for the Annex I
Sprague-Dawley	mg/kg bw/day in	-increased incidence of gray lung cysts in F2b	renewal: No
10 2	males; 0, 0.08, 1.9	offspring reared for 3 months (18 compared to 11	
M, F	and 37.7 mg/kg	in control group)	
25/	bw/day in females	25	
25/sex/group	F1: 0, 0.07, 1.7 and $37.0  mg/kg bw/day$	<u>25 ppm:</u> Parental:	
Study was	in males: 0, 0.08, 2.0	-clinical signs (hunched posture F0/F1)	
checked for	and 43.8 mg/kg	$h_{W}$ (P1 M· 1%· P2 M· 7%· P2 F 5%)	
compliance with	bw/day in females	$\downarrow$ 0 w (11 M. 1/0, 12 M. 7/0, 12 1 5/0)	
OECD TG 416		$\downarrow$ bw gain (P1 M: 2%, P2 M: 11%; P2 F: 6%)	
(2001) and following	The parents of both	Ofference	
Jouowing deviations were	the appropriate diets	<u>-increased incidence of gray lung cysts in F2b</u>	
noted:	for at least nine	offspring reared for 3 months (29 compared to 11	
i. No evaluation	weeks and then	in control group)	
of the oestrus	subjected to two		
cycles was	subsequent mating	<u>500 ppm:</u>	
performed for	trials. Fresh diets	Parental:	
ii No	presented weekly to	-clinical signs (F0/F1: nunched posture)	
examination of	the rats of all	↓ <b>bw</b> (P1 M: 4%; P2 M: <b>10%</b> ; P2 F <b>10%</b> )	
sperm	generations from	↓ <b>bw gain</b> (P1 M: 7%, P2 M: <b>11%</b> ; P2 F: 9%)	
parameters was	initiation (P1) or weaping (F1b $\rightarrow$ F2	$\downarrow$ <b>litter size</b> in F2a and F2b generations (mean	
either generation	F2b)	litter size born in F2a generation: 4 males and 5	
iii. Gestation	,	females compared to 6 males and 6 females in the	
length was not		generation: 5 males and 5 females compared to 7	
specified		males and 6 females in control group)	
iv. organs were			
v Vaoina testis		Offspring:	
epididymides,		-clinical signs (orange stained fur F2b offspring)	
seminal vesicles,		$\downarrow$ <b>bw</b> during lactation (F1a: 13% and 7% in males	
prostate and		and females, respectively; F1b: 14% and 9% in	
coagulating		males and females, respectively; F2a: 8% and 9%	
giana were not investigated		in males and females, respectively; F2b: 11% and 5% in males and females, respectively.	
microsconically		1 litter eine in EQ. and EQ.	
vi. Detailed		$\downarrow$ <b>Inter size</b> in F2a and F2b generations (mean	
testicular		itter size born in F2a generation: 4 males and 5	
histopathology		control group: mean litter size born in F2b	
was not		generation: 5 males and 5 females compared to 7	
performed		males and 6 females in control group)	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL (bold text)	Reference
vii. Postlactational ovary (primordial and growing follicles) histopathology was not performed viii. For the offspring, age at vaginal opening or PPS for the F1 and F2 was not determined		<ul> <li>-increased incidence of gray lung cysts in F2b offspring reared for 3 months (39 compared to 11 in control group)</li> <li>NOAEL parental and offsprings: 25 ppm (1.6 mg/kg bw/day)</li> <li>NOAEL reproductive toxicity: 500 ppm (37 mg/kg bw/day)</li> </ul>	
GLP: No			

#### Table 2.6.6.1-2. Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data				

#### Table 2.6.6.1-3. Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data				

# **2.6.6.1.1** Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility – generational studies

#### Two generation reproductive toxicity study (RAR Vol. 3, B.6.6.2/01)

The study is no GLP study and considered limited due to several deviations from the OECD TG 416. In the study, groups of 25 male and 25 female Sprague-Dawley rats received K-1616 (quinoclamine) in the diet at dose level up to 500 ppm (corresponding to 30.9 and 37.7 mg/kg bw/day in F0 males and females, respectively, and 37.0 and 43.8 mg/kg bw/day in F1 males and females, respectively) through two successive generations. Treatment with the test substance did not affect mating performance or fertility of the male and female parental animals and no consistent differences from control values were noted in comparisons of parental food consumption, survival rates and parturition indices or postnatal and postweaning survival. In addition, evaluations of the data obtained from foetuses taken by caesarean section did not reveal any findings indication teratogenic effects of the test substance at any of these concentrations. Differences from control group data noted at the high dose level (500 ppm) included lower growth period mean body weight values in the P1 (4% at week 13) and P2 (10% at week 9) generation males and P2 generation females (10% at week 9), reduced bodyweight gain in P1 (7%) and P2 (11%) generation males and P2 (9%) generation females, lower mean offspring weights at weaning in all filial generations (F1a: 13% and 7% in males and females, respectively; F1b: 14% and 9% in males and females, respectively; F2a: 8% and 9% in males and females, respectively; F2b: 11% and 5% in males and females, respectively), an increase in the observations of hunched appearance during the growth periods of both parental generations, and an increased incidence of gray lung cysts and orange-stained fur noted in the F2b offspring at necropsy. Mean litter size in F2a and F2b generations were also reduced at this dose level.

Differences noted to a lesser degree at the mid dose level (25 ppm) included slightly lower mean body weight values in the P1 (1% at week 13) and P2 (7% at week 9) generation males and P2 (5% at week 9) generation females at the last weighing interval of the growth periods, reduced bodyweight gain in P1 (2%) and P2 (11%) generation males and P2 (6%) generation females, an occasional slight increase in the observations of hunched appearance in both parental generations, and an increased incidence of gray lung cysts in the F2b offspring at necropsy.

Differences noted to a lesser degree at the low dose level (1 ppm) included slightly lower mean body weight values in the P1 (3%) and P2 (7%) generation males and P2 (4%) generation females at the last weighing interval of the growth periods, reduced bodyweight gain in P1 (4%) and P2 (11%) generation males and P2 (4%) generation females, an occasional slight increase in the observations of hunched appearance in both parental generations, and an increased incidence of lung cysts in the F2b offspring at necropsy.

Increased incidence of gray lung cysts was noted in the F2b offspring reared for three months (at 1 ppm: 18 compared to 11 in control group; at 25 ppm: 29 compared to 11 in control group; at 500 ppm: 39 compared to control group). The findings of gray lung cysts in the F2b offspring was dose related although the relevance of this finding is not clear. The finding was not observed in the offspring of the F1b generation reared for 5 weeks or in other available toxicological studies on quinoclamine. Thus, it seems to be a finding occurring in adult F2b animals including control animals. In the high dose group the incidence of gray cysts was 3.5 times higher when compared to controls, and therefore considered adverse. In the low and mid-dose groups the incidences were less marked (1.6 to 2.6 times higher when compared to controls) and not considered adverse in the absence of other effects in the offsprings at these dose levels.

The NOAEL for parental animals was set at 25 ppm (1.6 mg/kg bw/day) based on clinical signs (hunched posture) noted in P1 and P2 generation animals at 500 ppm (37 mg/kg bw/day), reduced body weight noted in P2 males and females at 500 ppm, and reduced bodyweight gain noted in P2 males at 500 ppm.

The NOAEL for offsprings was set at 25 ppm (1.6 mg/kg bw/day) based on reduced body weights at weaning in all filial generations noted at 500 ppm (37 mg/kg bw/day) and gray lung cysts noted in P2 offspring reared for 3 months at 500 ppm.

The NOAEL for reproductive toxicity was set at 500 ppm (37 mg/kg bw/day).

# 2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility

According to CLP Guidance Annex 1: 3.7.2.4.3, "Classification is not necessarily the outcome in the case...when there is only a small reduction in foetal/pup weight..."

# Two- generation reproductive toxicity study:

Administration of quinoclamine at dietary concentrations of up to 500 ppm (30.9 mg/kg bw/day) did not have any effect on mating performance or fertility. Parental adverse findings were noted at 500 ppm and included clinical signs (hunched posture, F0/F1), reduced bodyweight (P1 males: 4%, P2 animals of both sexes: 10%) and reduced bodyweight gain (P1 males: 7%, P2 males: 11%, P2 females: 9%). Reduced litter size was noted in the second generation at 500 ppm (mean litter size born in F2a generation: 4 males and 5 females compared to 6 males and 6 females in the control group; mean litter size born in F2b generation: 5 males and 5 females compared to 7 males and 6 females in control group), and reduced body weights were noted in the offspring during lactation (F1a: 13% and 7% in males and females, respectively; F1b: 14% and 9% in males and females, respectively; F2a: 8% and 9% in males and females, respectively; F2b: 11% and 5% in males and females, respectively). Furthermore, increased incidence of gray cysts in the lungs were noted in F2b offspring reared for 3 months (at 1 ppm: 18 compared to 11 in control group; at 25 ppm: 29 compared to 11 in control group; at 500 ppm: 39 compared to 11 in control group).

The observed effects in offspring noted at the highest dose level (500 ppm) (reduced bodyweight and reduced litter size) were not considered of concern for a classification for fertility effects, taken into account that the effects were seen in association with maternal toxicity (hunched posture and reduced body growth).

# 2.6.6.2 Adverse effects on development

Method, guideline,	Test substance, dose	Results	Reference
deviations if any,	levels duration of	- NOAEL/LOAEL (for parent, offspring	
species, strain, sex,	exposure	and for developmental effects)	
no/group		- target tissue/organ	
		- critical effects at the LOAEL	
Teratology range	ACN technical	Maternal effects:	RAR Vol. 3,
finding study	(Quinoclamine)	8 mg/kg bw/day:	B.6.6.2.1/01
		No treatment-related effects	
No guideline claimed	Purity: 98.1%		Anonymous 33 (1986)
in study		50 mg/kg bw/day:	Anonymous 33 (1989)
		-clinical signs (staining around eye)	(addendum)
Rat	0, 8, 50, 80, 200, 500		
	mg/kg bw/day	80 mg/kg bw/day:	Report No.: AKJ/2/86
Crl:CD (SD) BR		-clinical signs (stained urine, stained fur around	
		head)	

Table 2.6.6.2-1. Summary table of animal studies on adverse effects on development

Mothod and deline	Test substance dass	Domite	Deference
deviations if any	levels duration of	- NOAEL/LOAEL (for narent offsnring	Kelerence
species, strain, sex.	exposure	and for developmental effects)	
no/group	1	- target tissue/organ	
		- critical effects at the LOAEL	
F	Vehicle: 0.25% gum	- <b>bw loss</b> / $\downarrow$ <b>bw gain</b> (day 7-10: -3.5 g, day 10-	Report No.:
5/group	tragacanth	IS: 14% (II.S)) FC (Pregnancy Days 7-10: 27% Pregnancy	AKJ/2A/89 (addendum)
5/Broup	Gestation Days 7-17	Days 10-13: 20%, Pregancy Days: 13-17: 17%)	(uuuunin)
GLP: Yes		-macroscopic changes (enlarged spleen in one	New data for the
		female)	Annex I renewal: No
		200 mg/kg bw/day:	
		-mortality (one animal died, two animals were	
		killed in extremis)	
		-clinical signs (lethargy, hunched posture,	
		stained fur around anus, vagina, head)	
		- <b>bw loss/↓bw gain</b> (day 7-10: -19.8 g,	
		day 10-13:-1.5 g, day 13-17: 42% (n.s.))	
		LFC (Pregnancy Days 7-10: 52%, Pregnancy Days 10-13: 43%, Pregancy Days: 13-17: 29%)	
		-macroscopic changes (enlarged spleen and	
		adrenals, erosion of the stomach mucosa)	
		$\uparrow$ <b>post-implantation loss</b> (24.5% compared to 2.4% in controls)	
		2.4% in controls)	
		<u>500 mg/kg bw/day:</u>	
		-mortality (one animal died on day 10 of	
		killed in extremis on days 10 or 11 of	
		pregnancy)	
		-clinical signs (lethargy, hunched posture,	
		piloerection, stained urine, soft stained faeces,	
		<b>- bw loss</b> (-34 g, day 7-10)	
		↓FC	
		Developmental effects:	
		8 mg/kg bw/day:	
		No treatment-related effects	
		50 m = /les her/dem	
		No treatment-related effects	
		80 mg/kg bw/day:	
		↓mean foetal weight (8% n.s.)	
		200 mg/kg bw/day:	
		↑ postimplantation loss (24.5% compared to	
		2.4% in controls)	
		↓mean loetal weight (21%)	
		The study is acceptable as a range finding	
		study only. Due to low number of animals used	
		in the study it is not considered appropriate to	
Teratology study	ACN technical	Maternal effects:	RAR Vol. 3
- cratorogy study	(Quinoclamine)		B.6.6.2.1/02
No guideline claimed		5 mg/kg bw/day:	
in study	Purity: 98.1%	No treatment related effects	Anonymous 25 (1986)
Rat		20 mg/kg bw/day:	Report No.: AKJ/4/86

36.0 3 45			<b>D</b> 4
Method, guideline, deviations if any,	Test substance, dose levels duration of	Results - NOAEL/LOAEL (for parent, offspring and for developmental offsate)	Reference
species, strain, sex, no/group	exposure	- target tissue/organ	
	0.5.20 and 75 mg/kg	managaania ahangag (anlarged anlash ana	
Crl:CD (SD) BR	bw/day	dam)	New data for the Annex I renewal: No
F	Vehicle: 0.25% gum tragacanth	<u>75 mg/kg bw/day:</u> <b>- bw gain</b> (25% day 7-17)	
24/group	Gestation Days 7-17	$\downarrow$ FC (Gestation Days 7-10: 25%, Gestation Days 10-13: 14%)	
The study is		-macroscopic changes (enlarged spleen 4/24	
acceptable. It was		dams)	
checked for		(units)	
compliance with		Developmental effects:	
OECD TG 414 and		5 mg/kg bw/day:	
following deviations		No treatment-related effects	
were noted:			
<i>i. Exposure time in</i>		20 mg/kg bw/day:	
study was once daily		-abnormalities (innominate artery absent, one	
between adys / and		foetus)	
17 of pregnancy (the		-increased incidence of skeletal variants	
intended to examine		(skull: hyoid not ossified; vertebrae: thoracic	
solely the period of		centre one or more bilobed)	
organogenesis (e.g.			
days 5-15 in the		<u>75 mg/kg bw/day:</u>	
rodent) but also		$\downarrow$ foetal weight (7%)	
effects from		-abnormalities (innominate artery absent, four	
preimplantation,		foetuses; situs inversus, two foetuses; interrupt	
when appropriate,		aortic arch, one foctus)	
through the entire		-Increased incidence of skeletal variants	
period of gestation to		centre one or more bilobed/bipartite:	
the day before		sternebrae: 5 <sup>th</sup> and 6 <sup>th</sup> sternebrae not ossified	
caesarean section)		one or more bilobed bipartite or misaligned)	
ii. Treatment was not		one of more choced, cipatite of mounghed)	
extended (the		NOAEL maternal toxicity: 5 mg/kg bw/day	
guideline states: If		NOAEL developmental toxicity: 5 mg/kg	
preliminary studies,		bw/day	
when available, ab			
not indicate a nigh			
preimplantation loss			
treatment may be			
extended to include			
the entire period of			
gestation, from			
mating to the day			
prior to scheduled			
kill)			
iii. The choice of			
vehicle was not			
justified in study			
report			
GLP: Yes			
finding study	Quinoclamine	Maternal effects:	KAK Vol. 3, $D \in C \setminus 1/02$
linding study	Duritzy 00.00/	$\frac{10 \text{ mg/kg bW/day:}}{10 \text{ mg/kg bW/day:}}$	B.0.0.2.1/03
No guidaling alaimed	Punity: 99.0%	$\downarrow$ <b>Dw gain</b> (18%) (Day 0-20)	Anonymous 24 (2002)
in study		50  mg/kg hw/day:	Anonymous $54(2002)$
in study	0.10.50.100  mg/kg	$\frac{50 \text{ mg/Kg } 0\text{w/uay.}}{1 \text{ hw gain } (27\%) (Day 6-20)}$	Report No · 610/122
Rat	bw/day	Un gam (21/0) (Day 0-20)	D6154
t	5, au j	I	

Mothod and ditte	Tost substance 1.	Domita	Defenence
Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ	Reference
		- critical effects at the LOAEL	
Crl:CD (SD) IGSBR F 7/group GLP: Yes	Vehicle: 1% aqueous methylcellulose Gestation Days 6-19	↓FC (Days 4-20: 14%), Days 6-19: 14%, Days 19-20: 48%) ↑ <b>postimplantation loss</b> (6.2% compared to 2.8% in controls, mainly due to three deaths in one litter) ↑ <b>number of early intrauterine deaths</b> (mean number: 1.0 compared to 0.4 in control) ↓ <b>mean litter weight</b> (2%)	New data for the Annex I renewal: No
		100 mg/kg bw/day: ↓ bw gain (41%) (Day 6-20) ↓FC (Days 4-20: 21%), Days 6-19: 21%, Days 19-20: 30%) ↓ gravid uterus weight (17%) ↑ postimplantation loss (10.7% compared to 2.8% in controls) ↑ number of early intrauterine deaths (mean number: 1.2 compared to 0.4 in control) ↓ mean litter weight (16%) ↓ mean litter size (12 compared to 12.6 in control)	
		<u>Developmental effects:</u> <u>10 mg/kg bw/day:</u> ↓mean foetal weight (8%)	
		50 mg/kg bw/day: ↓mean foetal weight (11%) ↑postimplantation loss (6.2% compared to 2.8% in controls, mainly due to three deaths in one litter) ↑number of early intrauterine deaths (mean number: 1.0 compared to 0.4 in control) ↓mean litter weight (2%)	
		100 mg/kg bw/day: ↓mean foetal weight (12%) ↑postimplantation loss (10.7% compared to 2.8% in control) ↑number of early intrauterine deaths (mean number: 1.2 compared to 0.4 in control) ↓mean litter weight (16%) ↓mean litter size (12 compared to 12.6 in control)	
		The study is acceptable as a range finding study only. Due to low number of animals used in the study it is not considered appropriate to establish a NOAEL/LOAEL.	
Teratology study	Quinoclamine	Maternal effects:	RAR Vol. 3,
No guideline claimed in study	Purity: 99.0%	<u>5 mg/kg bw/day:</u> No treatment-related effects	B.6.6.2.1/04 Anonymous 26 (2002)
Rat	0, 5, 20, 75 mg/kg bw/day	20 mg/kg bw/day: -clinical signs (paddling of the forelimbs from Day 14 of gestation)	Report No.: 619/94- D6154

		[	
Method, guideline,	Test substance, dose	Results	Reference
deviations if any,	levels duration of	- NOAEL/LOAEL (for parent, offspring	
species, strain, sex,	exposure	and for developmental effects)	
no/group		- target tissue/organ	
		- critical effects at the LOAEL	
Crl:CD (SD) IGSBR		<b>↓bw gain</b> (Days 7-8: 62%, Days 17-19: 21%)	
	Vehicle: 1% aqueous	↓FC (Days 7-8: 14%, Days 9-12: 17%,	New data for the
F	methylcellulose	Days 12-15: 10%, Days 15-17: 12%,	Annex I renewal: No
		Days 17-19: 12%)	
24/group	Gestation Days 6-19	↓mean gravid uterus weight (15%)	
		<b>↓mean litter weight</b> (13%)	
GLP: Yes			
		75 mg/kg bw/day:	
The study is		-clinical signs (paddling of the forelimbs from	
acceptable. It was		Day 10, nose rubbing)	
checked for		↓ <b>bw gain</b> (Days 17-19: 41%)	
compliance with		<b>-bw loss</b> (Days 6-7: -4.6 g, Days 7-8: -2.6 g,	
updated OECD TG		Days 8-9: -0.4 g)	
414 (2001) and		↓FC (Days 4-6: 9%, Days 6-7: 27%,	
following deviations		Days 7-8: 44%, Days 8-9: 34%,	
were noted:		Days 9-12: 30%, Days 12-15: 17%,	
i. Exposure time in		Days 15-17: 13%, Days 17-19: 33%)	
study was once daily		↓mean gravid uterus weight (30%)	
between days 6 and		<b>post-implantation loss</b> (11% compared to	
19 of pregnancy (the		5% in control, n.s.)	
guideline is not		$\uparrow$ number of early intrauterine deaths (1.1	
intended to examine		compared to 0.7 in control)	
solely the period of		<b>I mean litter size</b> (12 compared to 14.8 in	
organogenesis (e.g.		control)	
days 5-15 in the		mean litter weight (29%)	
rodent) but also			
effects from		Developmental effects:	
preimplantation.			
when appropriate.		5 mg/kg bw/day:	
through the entire		No treatment-related effects	
period of gestation to			
the day before		20 mg/kg bw/day:	
caesarean section)		foetal weight (7%)	
ii. Treatment was not		mean litter weight (13%)	
extended (the		<b>†incidence of skeletal variations</b> (incomplete	
ouideline states: If		ossification of skull bone (frontal and nasal)	
preliminary studies		and unossified fifth sternebrae)	
when available do		and anospined man stemeorae)	
not indicate a high		75 mg/kg hw/day:	
potential for		foetal weight (12%)	
preimplantation loss		litter weight (29%)	
treatment may he		<b>post-implantation loss</b> (11% compared to	
extended to include		5% in control)	
the entire period of		the three implantation loss (17.4% compared to	
gestation from		8.6% in control but within current background	
mating to the day		data)	
nrior to scheduled		trumber of early intrauterine deaths (1.1	
kill)		compared to 0.7 in control)	
iii. The choice of		mean litter size (12 compared to 14.8 in	
vehicle was not		control)	
iustified in study		fincidence of skeletal variations (incomplete	
renort		ossification of skull bone (frontal and nasal)	
report		and unossified fifth sternehrae)	
		-malformations (subcutaneous ordema (one	
		foetus) retro-oesophageal aortic arch (one	
		foetus), kidney misshapen (one foetus)	
		hydropnephrosis (three foetuses))	
		NOAEL maternal: 5 mg/kg bw/day	
		1. S. ILL material. S mg/kg 0 W/day	

	[		
Method, guideline,	Test substance, dose	Results	Reference
deviations if any,	levels duration of	- NOAEL/LOAEL (for parent, offspring	
species, strain, sex,	exposure	and for developmental effects)	
no/group		- target tissue/organ	
		- critical effects at the LOAEL	
		NOAEL developmental: 5 mg/kg bw/day	
Teratology range	ACN (Quinoclamine)	Maternal effects:	RAR Vol. 3,
finding study		<u>8 mg/kg bw/day:</u>	B.6.6.2.2/01
	Purity: 98.1%	No treatment-related effects	
No guideline claimed	-		Anonymous 28 (1986)
in study		20 mg/kg bw/day:	-
	0, 8, 20, 50, 80/8 <sup>a</sup> ,	↑ <b>post-implantation loss</b> (31.1 compared to 8.7	Report No.: AKJ/1/86
Rabbit	200/20 <sup>a</sup> , 500/50 <sup>a</sup>	in control)	
New Zealand White			New data for the
	Vehicle: 0.25% gum	50 mg/kg bw/day:	Annex I renewal: No
F	tragacanth	-clinical signs (coloured urine)	
		↓bw (Day 10: 4%, Day 14: 5%)	
5/group	Gestation Days 6-18	↓FC (days 6-10)	
		<b>↑post-implantation loss</b> (61.0 compared to 8.7	
GLP: Yes		in control)	
		80/8 mg/kg bw/day:	
		-clinical signs (coloured urine)	
		bw (Day 7: 4%, Day 8: 3%, Day 10: 4%)	
		LFC (n.s.)	
		<b>post-implantation loss</b> (25.0 compared to 8.7	
		in control)	
		<u>200/20 mg/kg bw/day:</u>	
		-clinical signs (coloured urine)	
		↓bw (Day 7: 6%, Day 10: 6%)	
		↓FC (Day 6-10: 80%)	
		↑ <b>post-implantation loss</b> (30.0 compared to 8.7	
		in control)	
		500/50 mg/kg bw/day:	
		<b>-mortality</b> (both animals died, one died on day	
		9 and the other on day 10 of pregnancy) <sup>b</sup>	
		-clinical signs (lethargy, hunched posture, dark	
		coloured urine)	
		↓ <b>bw</b> (Day 8: 12%)	
		↓FC (Day 6-10: 80%)	
		Developmental officiate:	
		8 mg/kg bw/day:	
		No treatment related effects	
		The reaction related circets	
		20 mg/kg bw/day:	
		↑post-implantation loss (31.1 compared to 8.7	
		in control)	
		-malformations (spina bifida, two animals,	
		interrupted aortic arch major, one animal,	
		hindlimb left malrotated, one animal)	
		50 mg/kg bw/day.	
		<b>*post-implantation loss</b> (61.0 compared to 8.7	
		in control)	
		-malformations (interrupted aortic arch major	
		one animal, kidney left agenesis, one animal)	
		80 mg/kg bw/day:	
		<b>[] [] post-implantation loss</b> (25.0 compared to 8.7	
		in control)	

	r	r	r
Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ critical effects at the LOAEL	Reference
		200/20 mg/kg bw/day: ↑post-implantation loss (30.0 compared to 8.7 in control) The study is acceptable as a range finding study only. Due to low number of animals used in the study it is not considered appropriate to establish a NOAEL/LOAEL.	
Teratology study	ACN (Quinoclamine)	<u>Maternal effects:</u> 2.5 mg/kg bw/day:	RAR Vol. 3, B 6 6 2 2/02
No guideline claimed in study	Purity: 98.1%	No treatment-related effects	Anonymous 27 (1986)
Rabbit New Zealand White	0, 2.5, 7.5, 22.5 mg/kg bw/day	No treatment-related effects	Report No.: AKJ/3/86
F	Vehicle: 0.25% gum tragacanth	22.5 mg/kg bw/day: ↓ bw gain (Day 6-9: 0 kg compared to 0.08 kg	New data for the Annex I renewal: No
16/group	Gestation Days 6-18	in control, Days 0-28: 5%)	
The study is acceptable. It was checked for compliance with updated OECD TG 414 (2001) and following deviations were noted: i. Treatment was not extended (the guideline states: If preliminary studies, when available, do not indicate a high potential for preimplantation loss, treatment may be extended to include the entire period of gestation, from mating to the day prior to scheduled kill) ii. During the course of study relative humidity was within the range 54-76% (the guideline recommends the relative humidity not to exceed 70% other than during room cleaning) iii. The choice of wabiola was wast		Developmental effects:         2.5 mg/kg bw/day:         No treatment related effects         7.5 mg/kg bw/day:         No treatment-related effects         22.5 mg/kg bw/day:         ↓foetal weight (5% n.s.)         ↑increased incidence of skeletal variants         (increased no. of caudal centra ≤15         (84.9% compared to 59.9% in control))         -malformations (scoliosis, one animal, spina- bifida, three animals, anomalies of the aortic arch, two animals, sternebral fusions, three animals, hyperextension of limb or paw, one animal)         NOAEL maternal toxicity: 22.5 mg/kg bw/day         NOAEL developmental toxicity: 7.5 mg/kg bw/day	

	r	[	r
Method, guideline, deviations if any.	Test substance, dose levels duration of	Results - NOAEL/LOAEL (for parent offspring	Reference
species, strain, sex,	exposure	and for developmental effects)	
no/group		- target tissue/organ	
ingtified in study		- critical effects at the LOAEL	
justifiea in stuay report			
report			
CLD V			
GLP: Yes			
Teratology range	Quinoclamine	Maternal effects:	RAR Vol. 3,
finding study		5 mg/kg bw/day:	B.6.6.2.2/03
No guidalina alaimad	Purity: 99.0%	No treatment related effects	Anonymous 25 (2002)
in study	0, 5, 17.5, 30 mg/kg	17.5 mg/kg bw/day:	Anonymous 55 (2002)
	bw/day	<b>↓bw change</b> (Days 7-28: 12% of controls)	Report No.: 619/122-
Rabbit		↓FC	D6154
Crl.NZW/Kbl BR	Vehicle: 1% aqueous	30 mg/kg bw/day:	New data for the
	methyleenulose	-abortion (one animal, on Day 29)	Annex I renewal: No
F	Gestation Days 7-28	↓ <b>bw change</b> (Days 7-28: 10% of controls)	
<i></i>		↓FC (Days 7-28: 2.4%, Days 28-29: 4%)	
//group		$\uparrow$ <b>post-implantation loss</b> (22.4% compared to 14.9% in control)	
GLP: Yes		↑number of late intrauterine deaths (1.6	
		compared to 1.0 in control)	
		↓mean litter weight (6%)	
		Developmental effects:	
		5 mg/kg bw/day:	
		No treatment-related effects	
		17.5  mg/kg hw/day	
		No treatment related effects	
		20 mg/kg hu/dau	
		<u>-abortions (one animal on Day 29)</u>	
		↑ <b>post-implantation loss</b> (22.4% compared to	
		14.9% in control)	
		fnumber of late intrauterine deaths	
		mean litter weight (6%)	
		↓mean foetal weight (3%)	
		The study is accortable as a survey for disc	
		study only. Due to low number of animals used	
		in the study it is not considered appropriate to	
		establish a NOAEL/LOAEL	
Teratology study	Ouinoclamine	Maternal effects:	RAR Vol. 3.
Teratorogy states	2 unio unio	5 mg/kg bw/day:	B.6.6.2.2/04
OECD 414	Purity: 99.0%	No treatment related effects	
Rabbit	0 5 17 5 30 mg/kg		Anonymous 29 (2002)
1.uoon	bw/day	17.5 mg/kg bw/day	Report No.: 619/155-
Crl.NZW/Kbl BR		<b>↓bw change</b> (bw change Days 12-15: 67% of	D6154
E	Vehicle: 1% aqueous	control)	
Г	memyicentulose	compared to 9.5 in control)	New data for the
24/group	Gestation Days 7-28	r	Annex I renewal: No
		<u>30 mg/kg bw/day:</u>	

Method, guideline, species, strain, ser, nogroup         Reference           The study follows OCD TG 414 except for following deviations if any comparison of the special field on Day 18 of gestation (the guideline recommends ator no Day 7 of gestation (the guideline recommends ator no Day 6 of gestation)		r		ľ
deviations if any, species, strain, molgroup levels duration of species, strain, species, species, species, species,	Method, guideline,	Test substance, dose	Results	Reference
species, strain, sex, no/group no/	deviations if any,	levels duration of	- NOAEL/LOAEL (for parent, offspring	
indigroup       - urget tissue/organ         - origited Herics at the LOAKL         The study follows         GED 76 of following         deviations:         animate         Losing of animate         Diversitions:         animate         Diversitions:         Diversitions: <t< td=""><td>species, strain, sex,</td><td>exposure</td><td>and for developmental effects)</td><td></td></t<>	species, strain, sex,	exposure	and for developmental effects)	
• - critical effects af the LOARL         The study follows:         0ECD TG 414         gestation?         1 bw change (Days 1.2-15: 0 kg compared to 0.12 kg in control, Days 4.29: 46% of control)         started on Days 7 of gestation (the guideline         deviations:         1 Do sing of control, Days 4.29: 46% of control)         1 PC         gestation?         gestation?         1 Do sing of control, Days 4.29: 46% of control)         recommends         0 D 2 kg in control, Days 4.29: 46% of control)         gestation?         gestation?         in control)         terr of polowing         gestation?         in control)         is control         gestation?         in control         in control         gestation?         in control         in control         gestation?         in the range 30-80%         (the guideline         chards the recommeds the relative humidity not         to exceed 70% other than during room         chards the conpared to 2.5 in control)         interased incidence of abnormal terminal increased incidence of abnormal terminal increased incidence of abnormal terminal increased incidence of abnormal terminal i	no/group	-	- target tissue/organ	
The study follows       -mortality (one female killed on Day 18 of gestation?)         OECD TG 414       gestation?)         Losing of animals started on Day 7 of gestation (he guideline recommends dations: 2.4.9.13 compared to 4.8/10 in control)       IFC         prest-implantation loss (%-No. of affected dams: 2.4.9/13 compared to 4.8/10 in control)       IFC         prest-implantation loss (%-No. of affected dams: 2.4.9/13 compared to 4.8/10 in control)       IFC         in Dark pi control, Dary 4.2.9: 4.4% of control)       Ifer intrauterine deaths (1.4 compared to 0.3 in control)         in control)       Inter size (7.8 foctuses per female compared to 9.5 in control)       Inter size (7.8 foctuses per female compared to 9.5 in control)         in exceed 70% other       Inter size (8.4 foctuses per female compared to 9.5 in control)       Inter size (8.4 foctuses per female compared to 9.5 in control)         inclusing       Immentiliter size (8.4 foctuses per female compared to 9.5 in control)       Inter size (8.4 foctuses per female compared to 9.5 in control)         increased incidence of abnormal terminal canadal vertebrase, man % foctus: 5.6% compared to 2.3% in control)       Inter size (7.8 foctuses per female compared to 9.5 in control)         gate field in study       Inter size (7.8 foctuses per female compared to 0.3 in control)       Inter size (7.8 foctuses per female compared to 0.2.3% in control)         III: The whick widay:       Inter size (7.8 foctuses per female compared to 0.3 in control)       Inter size (7.8 foctuses pe	8		- critical effects at the LOAEL	
International of the termine knine of the 2y it of the second for following deviations:       Ib we change (Days 12-15: 0 kg compared to 0.12 kg in control) Days 4-29: 46% of control)         i. Dosing of animals started on Day 14 (Days 12-15: 0 kg compared to 0.12 kg in control). Days 4-29: 46% of control)       If C         gestation (the guideline dams: 24-9.13 (Songmat to 4.81 (O in control))       If C         gestation)       in control.       Days 4-29: 46% of control)         start on Day 6 of gestation)       in control)       In control)         in control)       Internitive method (1.4 compared to 0.2 in control)       Internitive method (1.4 compared to 0.3 in control)         ii. During the course       Internitive registrol       Internitive registrol         gestation)       ii. Control)       Internitive registrol       Internitive registrol         ii. Buring the course       Internitive registrol       Internitive registrol       Internitive registrol         iii. Buring the course       Internitive registrol       Internitive registrol       Internitive registrol         iii. Buring the course       Internitive registrol       Internitive registrol       Internitive registrol         iii. Buring the course       Internitive registrol       Internitive registrol       Internitive registrol         iii. Buring the course       Internitive registrol       Internitive registrol       Internitive registro	The study follows		mortality (one female killed on Day 18 of	
ORLD 100474       Igestition (Buysking)         Low (Charge Charge Charge)       Igestition (He         deviations:       1.0 Key of control)         started on Day 7 of       IPC         gestation (He       Igestition (He         guideline       1.0 Key of control)         recommends       1.0 Large in control)         administration to       0.2 in control)         start on Day 6 of       1.0 Key in control)         gestation (He       1.0 Key in control)         gestation (He       1.0 Key in control)         gestation (He       1.0 Key in control)         gestation of the course       1.0 Key in control)         gestation (He       1.0 Key in control)         incontrol       1.0 Key in control)         incontrol       1.0 Key in control)         individual relative       1.0 Key in control)         interversite       1.0 Key in control)         interversit	OECD TC 414		asstation <sup>6</sup> )	
cccoping of politiving       1. Do Sing of animals         i. Dosing of animals       0.12 kg in control, Days 4-29: 4% of control)         started on Days 7 of gestation (the guideline dums: 24.9/13 compared to 4.8/10 in control)       1PC         recommends       1PC         administration to       0.21 in control)         start on Days 6 of gestation (the guideline dums: 24.9/13 compared to 4.8/10 in control)       1In the intrauterine deaths (1.4 compared to 0.3 in control)         ii. During the course       Imean litter size (7.8 loctuses per female compared to 9.5 in control)         jiiter weight (24%)       Iiiter weight (24%)         the guideline       Developmental offects: 5 mg/kg bw/day:         recommends the record 70% other than during room control)       Imman litter size (8.4 foctuses per female compared to 9.5 in control)         settiff in study       increased incidence of abnormal terminal cudad vertebrae, mean % foctus: 5.0% compared to 2.3% in control)         gestation)       1.3 mg/kg bw/day:         increased incidence of abnormal terminal cudad vertebrae, mean % foctus: 5.0% compared to 0.2 in control)         gestation for the size (7.8 loctuses per female compared to 0.2 in control)         inter weight (24%)       1         gestation study       increased incidence of abnormal terminal cudad vertebrae, mean % foctus: 5.0% compared to 0.2 in control)         gestating)       1 <td< td=""><td></td><td></td><td>(D - 4.20, 70)</td><td></td></td<>			(D - 4.20, 70)	
Ibw change (Days 12-15: 0 kg compared to 0.12 kg in control, Day 4-29: 46% of control) FC       include         started on Day 7 of gestation (the guideline       include include include include include include include damistration to start on Day 6 of gestation (the course of study relative       include include include include include include include include include include include include include include include include	except for following		10 (Days 4-29: 7%)	
i. Doxing of animals       0.12 kg in control, Days 4-29; 46% of control)         started on Day 7 of gestation (the guideline dams: 24-9/13 compared to 4-8/10 in control)       iPC         recommends       tearty intrauterine deaths (1.0 compared to 0.3 in control)         administration to administration to gestation)       iIate intrauterine deaths (1.4 compared to 0.3 in control)         in Dary 6 of gestation)       iInter size (7.8 foctuses per female control)         in Dary 6 of gestation)       iInter size (7.8 foctuses per female control)         in Dary 6 of gestation)       iInter size (7.8 foctuses per female control)         indiverse of the guideline       Developmental effects:         recommends the relative humidity not       No treatment related effects         to exceed 70% other       increased incidence of abornmal terminal control)         increased incidence of sobornmal terminal cond verbare, neam % foctus: 5.6%       compared to 2.3 in control)         compared to 2.3 in control)       increased incidence of abornmal terminal cond verbare, neam % foctus: 5.6%         compared to 2.3 in control)       increased incidence of abornmal terminal control)         feed dams: 24.913 compared to 0.3 in control)       increased incidence of abornmal terminal cond verbare. Incomplete ossification of to 5.5 in control)         inter prot       175 mg/kg bw/day;       tpost-implantation loss (%/No. of affected dams: 24.913 compared to 0.3 in control)	deviations:		<b>bw change</b> (Days 12-15: 0 kg compared to	
started on Day 7 of gestation (the guideline recommends administration to start on Day 6 of gestation (b) in control) in control) in control in	i. Dosing of animals		0.12 kg in control, Days 4-29: 46% of control)	
gestation (the guideline prost-implantation loss (%/No. of affected dams 24.913 compared to 4.8.90 in control) recommends 0.2 in control) (tearly intrauterine deaths (1.4 compared to 0.3 in control) in control) (the guideline compared to 9.5 in control) (the guideline compared to 9.3 in control) (the guideline compared to 9.3 in control) (the guideline compared to 9.3 in control) (the guideline compared to 2.3% in control) (the guideline compared to 9.4 in control) (the guideline compared to 9.5 in control) (the guideline compared to 9	started on Day 7 of		↓FC	
guideline dams: 24.9/13 compared to 4.8/10 in control) recommends administration to administration to administration to arr on Day 6 of gestation] in Curring the course gestation] in Curring the course gestation] in Curring the course gestation] humidity was within the range 30.80% (the guideline recommends the recommends the recommend the subscience of vehicle was not justified in study report caudal vertebrae, mean % foetus: 5.6% compared to 2.5% in control) tearly intratuterine deaths (1.4 compared to 0.2 in control) the intratuterine deaths (1.4 compared to 0.3 in control) the intratuterine deaths (1.4 compared to 0.3 in control) the intratuterine deaths (1.4 compared to 0.3 in control) the intratuterine deaths (1.4 compared to 0.4 in control) the inter site (7.8 foetuses per female compared to 9.5 in control) the inter site (7.8 foetuses per female compared to 9.5 in control) the inter site (7.8 foetuses per female compared to 9.5 in control) the inter site (7.8 foetuses per female compared to 9.5 in control) the inter site (7.8 foetuses per ternal compared to 9.5 in control) th	gestation (the		<b>↑post-implantation loss</b> (%/No. of affected	
recommends       tearly intrauterine deaths (1.0 compared to 0.3 in control)         start on Day 6 of gestation)       (1 act intrauterine deaths (1.4 compared to 0.3 in control)         in During the course of study relative compared to 9.5 in control)       (1 mean litter size (7.8 foctuses per female compared to 9.5 in control)         in During the course of study relative humidity was within       (1 mean litter size (7.8 foctuses per female compared to 9.5 in control)         in the range 30-80%       (1 mean litter size (8.4 foctuses per female compared to 9.5 in control)         in exceed 70% other       (1 mean litter size (8.4 foctuses per female compared to 9.3 in control)         in exceed 70% other       (1 mean litter size (8.4 foctuses per female compared to 9.3 in control)         increased incidence of abnormal terminal caudal vertebras, mean % foctus: 5.6%       compared to 9.3 in control)         verifie was not       -malformation fox (%No, of affected dams: 24.9/13 compared to 0.3 in control)         GLP: Yes       30 mg/kg bw/day:         ''''''''''''''''''''''''''''''''''''	guideline		dams: 24.9/13 compared to 4.8/10 in control)	
administration to       0.2 in control)         start on Day 6 of gestation)       7 Inter intrauterine deaths (1.4 compared to 0.3 in control)         in control       in control)         in the range 30-80%       (Metal to 9.5 in control)         (the range 30-80%)       (Metal to 9.5 in control)         (the death of the range 30-80%)       (Metal to 9.5 in control)         (the reading room control to 9.5 in control)       (Metal to 9.5 in control)         (the death of the range 30-80%)       (Metal to 9.5 in control)         (else was not justified in study)       (metal to 9.5 in control)         (add) vertebrae, mean % foctus: 5.6%       (compared to 2.3% in control)         (due to 1.4 compared to 0.3 in control)       (Metal the trattartine deaths (1.4 compared to 0.3 in control)         (add) vertebrae, mean % foctus: 5.6%       (Ompared to 9.5 in control)         (due to 1.4 compared to 0.4 (1.4 compared to 0.3 in control)       (Metal to 1.4 (24%))         (additional	recommends		<b>↑early intrauterine deaths</b> (1.0 compared to	
start on Day 6 of gestation) in control) jmean litter size (7.8 foctuses per female compared to 9.5 in control) humidity way within the range 30-80% (the guideline recommends the commends the second 70% other than during room cleaning) jmean litter size (8.4 foctuses per female compared to 9.5 in control) is created 70% other than during room cleaning) jmean litter size (8.4 foctuses per female compared to 9.5 in control) while way not particle way not part particle way not part part part particle way not part part part part part part part part	administration to		0.2 in control)	
gestation) in control) i. During the course of study relative humidity was within the range 30-80% (the guideline recommends the recommends the recom	start on Day 6 of		<b>†late intrauterine deaths</b> (1.4 compared to 0.3	
generation       jmean litter size (7.8 foctuses per female compared to 9.5 in control) humidity way within the range 30-80% (the guideline       jmean litter size (7.8 foctuses per female compared to 9.5 in control)         pevelopmental effects:       5 mg/kg bw/day:         recommends the recommends the recommends the in creased incidence of abormal terminal caudal vertebrae, mean % foctus: 5.6% compared to 2.5% in control)         uestified in study       -malformation loss (%/No. of affected dams: 24.9/13 compared to 4.8/10 in control)         GLP: Yes       30 mg/kg bw/day: nortrol)         GLP: Yes       30 mg/kg bw/day: nortrol)         in control)       1 mean litter size (7.8 foctuses per female compared to 2.3% in control)         file       30 mg/kg bw/day: nortrol)         generation       -malformation loss (%/No. of affected dams: 24.9/13 compared to 4.8/10 in control)         file       -malformation loss (%/No. of affected dams: 24.9/13 compared to 0.3 in control)         jmean litter size (7.8 foctuses per female compared to 9.5 in control)       1         jmean litter size (7.8 foctuses ser female compared to 9.5 in control)       1         ifter size (7.8 foctuses per female compared to 9.5, in control)       1         jmean litter size (7.8 foctuses per female compared to 2.3% in control)       1         incensed incidence of abormal terminal caudal vertebrae, cervical vertebral certra)       -malformations (hydronephrosis, 2 animals; increased incidence of abormal termi	aestation)		in control)	
II. During the Converse       pincan fuely size (7.5 incontrol)         humidity was within       ther arage 30-80%         (the guideline       Developmental effects:         recommends the       5 mg/kg bw/day:         relative humidity not       No treatment related effects         to exceed 70% other       17.5 mg/kg bw/day:         relative humidity not       No treatment related effects         to exceed 70% other       17.5 mg/kg bw/day:         pincan futter size (8.4 foctuses per female       0         (ii). The choice of       - malformations (hydronephrosis, one animal, increased incidence of abnormal terminal         report       caudal vertebra, mean % foctus: 5.6%         compared to 2.3% in control)       30 mg/kg bw/day:         Tpost-implantation loss (%/No. of affected       dams: 2.49/13 compared to 4.8/10 in control)         fearly intrauterine deaths (1.4 compared to 0.3 in control)       1         fmean filter size (7.8 foctuses per female       compared to 9.5 in control)         j. mean filter size (7.8 foctuses asymmetric ossification of sternebra, asymmetric ossification of cervical vertebral central         sight fusion of sternebra, asymmetric ossification of cervical vertebral central         ocsification of cervical vertebral central         arcmal vertebra, neare % foctus: 5.4% compared to 2.3%, no control         j. fact formations	ii During the course		mean litter size (7.8 features per female	
c) statute       Compared to 9.5 in Control)         humidity was within       Jitter weight (24%)         the guideline       Smg/kg bw/day;         recommends the       Smg/kg bw/day;         relative humidity not       No treatment related effects         to exceed 70% other       17.5 mg/kg bw/day;         itil. The choice of       compared to 9.5 in control)         yearing the was not       -mailformations (hydronephrosis, one animal, increased incidence of abnormal terminal caudal vertebrae, mean % foctus; 5.6%         compared to 2.3% in control)       -mailformation (by/sonephrosis, one animal, increased incidence of abnormal terminal caudal vertebrae, mean % foctus; 5.6%         GLP: Yes       30 mg/kg bw/day;         GLP: Yes       30 mg/kg bw/day;         The intrauterine deaths (1.4 compared to 0.3 in control)         time mitter size (7.8 foctuses per female compared to 0.3 in control)         time mitter size (7.8 foctuses per female compared to 0.3 in control)         time mitter size (7.8 foctuses per female compared to 0.3 in control)         time mitter size (7.8 foctuses per female compared to 0.3 in control)         time mitter size (7.8 foctuses per female compared to 0.3 in control)         time mitter size (7.8 foctuses per female compared to 0.3 in control)         time mitter size (7.8 foctuses in control)         time for thy intrauterine deaths (1.4 compared to 0.3 in con	a. During the course		$\downarrow$ incar fitter Size (7.6 focuses per female	
numinaty wis within       jutter weight (24%)         the range 30.80%       Developmental effects:         ie commends the       Sing/kg bw/day:         recommends the       No treatment related effects         ie commends in the choice of       image in compared to 9.5 in control)         yehicle was not       -mailformations (hydronephrosis, one animal, increased incidence of abnormal terminal caudal vertebrar, mean % foctus: 5.6%         report       compared to 2.3% in control)         GLP: Yes       30 mg/kg bw/day:         7 post-implantation loss (%/No. of affected dams: 24.9/13 compared to 4.8/10 in control)         1 fair intrauterine deaths (1.0 compared to 0.3 in control)         1 fair weight (24%)         1 specific for star variations (kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior formalelle, inccompleto osification of forntal and maxilla bones, slight fusion of screebra, asymmetric ossification of cervical vertebral, emans (hydronephrosis, 24 animals; increased incidence of abnormal terminal caudal vertebrar, emans (bidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior formatelle, inccompleto osification of foretus: 6.4% compared to 2.3% in control)         1 faiter weight (24%)       1 specific foretal vertebrar, emans (foretus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial certebral arch, one foctus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial certebral arch, one foctus: 5.4% compared to 0.0% in control) <td>of study relative</td> <td></td> <td>Compared to 9.5 in control)</td> <td></td>	of study relative		Compared to 9.5 in control)	
Interange 30-80%         Developmental effects:         recommends the         relative humidity not         to exceed 70% other         than during room         (cleaning)         jumean litter size (8.4 foctuses per female compared to 9.5 in control)         vehicle was not         justified in study         recased incidence of abnormal terminal         report         GLP: Yes         30 mg/kg bw/day:         7post-implantation loss (%/No. of affected dams: 24.913 compared to 0.3 in control)         report         GLP: Yes         30 mg/kg bw/day:         7post-implantation loss (%/No. of affected dams: 24.913 compared to 0.3 in control)         rementitier size (7.8 foctuses per female compared to 9.5 in control)         juffer in size (7.8 foctuses per female compared to 9.5 in control)         juffer of size (7.8 foctuses per female compared to 9.5 in control)         juffer of size (7.8 foctuses per female compared to 9.5 in control)         juffer of size (7.8 foctuses per female         comord)         juffer of size (7.8 foctuses per female         compared to 9.2 in control)         juffer of size (7.8 foctuses per female         compared to 9.3 in control)         juffer of size (7.8 foctuses per female	numiaity was within		↓Intter weight (24%)	
(the guideline       Developmental effects:         recommends the       Sm2kg bw/day:         relative humidity not       No treatment related effects         to exceed 70% other       1.7.5 mg/kg bw/day:         (lmean litter size (8.4 foctuses per female       compared to 9.5 in control)         vehicle was not       -mailformations (hydronephrosis, one animal, increased incidence of abnormal terminal         report       caudal vertebra, mean % foctus: 5.6%         Compared to 2.3% in control)       Sompared to 8.1% in control)         GLP: Yes       30 mg/kg bw/day:         7 post-implantation loss (%/No. of affected       dams: 24.9/13 compared to 4.8/10 in control)         1 fair intrauterine deaths (1.4 compared to 0.3 in control)       1 mean litter size (7.8 foctuses per female         compared to 9.5 in control)       1 jlitter weight (24%)         1 specific footal variations (kidney cavitation, additional liver lobe, cervical vertebra, easymmetric       ossification of control and maxilla         bone, slight fusion of stemebrae, asymmetric       ossification of corteol and maxilla       damsilla         acaudal vertebrae, mean % foetus: 6.4%       compared to 2.3% in control; mishapen nasal       bone (8.0%, not present in historial ctr data at time for study; misaligned thoracic vertebral arch, one foetus; foreased incidence of absent frontalt, mean % foetus: 6.4%       compared to 2.3% in control; mishapen nasal         bon	the range 30-80%			
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then during room       17.5 mg/kg bw/day:         imman litter size (8.4 foctuses per female       imman litter size (8.4 foctuses per female)         whicle was not       -malformations (hydronephrosis, one animal, increased incidence of abnormal terminal caudal vertebrae, mean % foctus: 5.6%         compared to 2.3% in control)       GLP: Yes         30 mg/kg bw/day:       1post-implantation loss (%/No. of affected)         dams: 24.9/13 compared to 4.8/10 in control)       1early intrauterine deaths (1.0 compared to 0.3 in control)         1 Jumean litter size (7.8 foctuses per female compared to 9.5 in control)       1jlitter weight (24%)         1 specific foctal variations (kidney cavitation, additional liver lobe, cavical rennant of thymus, lengthened anterior fontanelle, incomplete ossification of crevical rennant of thymus, lengthened anterior fontanelle, increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4%         compared to 2.3% in control)       -malformations (kidney cavitation, additional liver lobe, cervical rennant of thymus, lengthened anterior fontanelle, increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4%         compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctri data at time for study; misaligned thoracic vertebral arch, one foetus; 8.9% compared to 0.0% in control; misshapen nasal bone (8.0%, not present in historial ctri data at time for study; misaligned thoracic vertebral arch, one foetus; 8.9% compared to 0.0% in control)         NOAEL developmental toxicity: 5 mg/kg bw/day       NOAEL developmental toxicity: 5 mg/kg bw/day	to exceed 70% other			
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webicle was not justified in study       -malformations (hydronephrosis, one animal, increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 5.6% compared to 2.3% in control)         GLP: Yes       30 mg/kg bw/day: Tpost-implantation loss (%/No. of affected dams: 24.9/13 compared to 4.8/10 in control) tearly intrauterine deaths (1.0 compared to 0.2 in control)         Plate intrauterine deaths (1.4 compared to 0.3 in control)       Imean litter size (7.8 foetuses per female compared to 2.95 in control)         Jitter weight (24%)       f specific foetal variations (kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior fontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebrai central - malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control)         NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day	iii. The choice of		compared to 9.5 in control)	
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30 mg/kg bw/day:         ↑ post-implantation loss (%/No. of affected dams: 24.9/13 compared to 4.8/10 in control)         ↑ early intrauterine deaths (1.0 compared to 0.2 in control)         ↑ late intrauterine deaths (1.4 compared to 0.3 in control)         ↓ mean litter size (7.8 foctuses per female compared to 9.5 in control)         ↓ Jitter weight (24%)         ↑ specific foetal variations (kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior fontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebral centra)         - malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial cr dat at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control)         NOAEL developmental toxicity: 5 mg/kg bw/day	GLP: Tes			
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<ul> <li>0.2 in control)</li> <li>↑late intrauterine deaths (1.4 compared to 0.3 in control)</li> <li>↓mean litter size (7.8 foetuses per female compared to 9.5 in control)</li> <li>↓litter weight (24%)</li> <li>↑ specific foetal variations (kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior fontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebral centra)</li> <li>- malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); missligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control)</li> <li>NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day</li> </ul>			↑early intrauterine deaths (1.0 compared to	
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in control) ↓mean litter size (7.8 foetuses per female compared to 9.5 in control) ↓litter weight (24%) ↑ specific foetal variations (kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior fontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebral centra) - malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus; increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control) NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			$\uparrow$ late intrauterine deaths (1.4 compared to 0.3)	
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<ul> <li>↓litter weight (24%)</li> <li>↑ specific foetal variations (kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior fontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebral centra)</li> <li>- malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control)</li> <li>NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg</li> </ul>			compared to 9.5 in control)	
<ul> <li>\$ specific foctal variations (kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior fontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebral centra)</li> <li>- malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control)</li> <li>NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg</li> </ul>			↓litter weight (24%)	
<ul> <li>additional liver lobe, cervical remnant of thymus, lengthened anterior fontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebral centra)</li> <li>malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control)</li> <li>NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day</li> </ul>			↑ specific foetal variations (kidnev cavitation.	
<ul> <li>thymus, lengthened anterior fontanelle,</li> <li>incomplete ossification of frontal and maxilla</li> <li>bones, slight fusion of sternebrae, asymmetric</li> <li>ossification of cervical vertebral centra)</li> <li>malformations (hydronephrosis, 2 animals;</li> <li>increased incidence of abnormal terminal</li> <li>caudal vertebrae, mean % foetus: 6.4%</li> <li>compared to 2.3% in control; misshapen nasal</li> <li>bone (8.0%, not present in historial ctr data at</li> <li>time for study); misaligned thoracic vertebral</li> <li>arch, one foetus; increased incidence of absent</li> <li>frontal, mean % foetus: 8.9% compared to</li> <li>0.0% in control)</li> </ul> NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg			additional liver lobe, cervical remnant of	
<ul> <li>incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebral centra)</li> <li>- malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control)</li> <li>NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg</li> </ul>			thymus, lengthened anterior fontanelle	
<ul> <li>Incompact obstitution of itomat and matha</li> <li>bones, slight fusion of sternebrae, asymmetric</li> <li>ossification of cervical vertebral centra)</li> <li>- malformations (hydronephrosis, 2 animals;</li> <li>increased incidence of abnormal terminal</li> <li>caudal vertebrae, mean % foetus: 6.4%</li> <li>compared to 2.3% in control; misshapen nasal</li> <li>bone (8.0%, not present in historial ctr data at</li> <li>time for study); misaligned thoracic vertebral</li> <li>arch, one foetus, increased incidence of absent</li> <li>frontal, mean % foetus: 8.9% compared to</li> <li>0.0% in control)</li> <li>NOAEL maternal toxicity: 5 mg/kg bw/day</li> <li>NOAEL developmental toxicity: 5 mg/kg</li> </ul>			incomplete ossification of frontal and maxilla	
<ul> <li>boncs, signification of serifcorae, asymmetric</li> <li>ossification of cervical vertebral centra)</li> <li>malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4%</li> <li>compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control)</li> <li>NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg</li> </ul>			hones slight fusion of sternehrae asymmetric	
<ul> <li>malformations (hydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control)</li> <li>NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg</li> </ul>			ossification of cervical vertebral central	
<ul> <li>- mator mations (nydronephrosis, 2 animals; increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control)</li> <li>NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg</li> </ul>			molformations (hydronenbrasis 2 animal-	
Increased incidence of abnormal terminal caudal vertebrae, mean % foetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control) NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			- mation mations (nyuronephrosis, 2 animals;	
caudal vertebrae, mean % toetus: 6.4% compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control) NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			increased incidence of abnormal terminal	
compared to 2.3% in control; misshapen nasal bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control) NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			caudal vertebrae, mean % foetus: 6.4%	
bone (8.0%, not present in historial ctr data at time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control) NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			compared to 2.3% in control; misshapen nasal	
time for study); misaligned thoracic vertebral arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control) NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			bone (8.0%, not present in historial ctr data at	
arch, one foetus, increased incidence of absent frontal, mean % foetus: 8.9% compared to 0.0% in control) NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			time for study); misaligned thoracic vertebral	
frontal, mean % foetus: 8.9% compared to 0.0% in control) NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			arch, one foetus, increased incidence of absent	
0.0% in control) NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			frontal, mean % foetus: 8.9% compared to	
NOAEL maternal toxicity: 5 mg/kg bw/day NOAEL developmental toxicity: 5 mg/kg bw/day			0.0% in control)	
NOAEL developmental toxicity: 5 mg/kg			NOAFI maternal toxicity: 5 mg/kg bw/dev	
hw/day			NOAFL developmental toxicity: 5 mg/kg	
			hw/day	

<sup>a</sup>: The original design of the study was to dose five animals in each group at 80, 200 or 500 mg/kg bw/day. Because of severe toxicity elicited at the highest dose level, the doses were reduced after one dose to 8, 20 or 50 mg/kg bw/day, respectively.

Because mating was staggered over two days, half of the animals in each group received one dose at the initial high dose level and on subsequent days were dosed at the lower level (abbr. "a"). The other half of the animals in each group received the lower dose level throughout the dosing period.

<sup>b</sup>: At necropsy these animals showed pale liver, abnormal spleen and dark intestinal contents.

<sup>c</sup>: One pregnant high dose group female was killed on Day 18 of gestation following severe inappetence and body weight loss and clinical observation of red discharge from the urogenitial region. Necropsy examination did not reveal any macroscopic abnormalities.

#### Table 2.6.6.2-2. Summary table of human data on adverse effects on development

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data				

Type of	Test	Relevant	Observations	Reference
study/data	substance	information about		
•		the study (as		
		applicable)		
Dermal	Quinoclamine	The study was	Maternal effects:	RAR Vol. 3, B.6.8.2/01
embryo-		performed to		
foetal	Purity: 97.7%	investigate the effects	<u>5 mg/kg bw/day:</u>	Anonymous 30 (1996)
development		of the test article on	-clinical signs (coloured urine)	
study	5, 100, 600	the embryonic and	-macroscopical changes (reddish	Report No.: 1312-1416-001
	mg/kg	fetal development of	discolouration of treated skin)	
Rat	bw/day	the rat when		New data for the Annex I
		administered during	<u>100 mg/kg bw/day:</u>	renewal: No
In house	Vehicle: 1%	the period of	-clinical signs (encrusted skin,	
method	Tween 80	organogenesis. Three	coloured urine)	
		groups of twenty five	-macroscopical changes (reddish	
GLP: Yes	Day 6 to 15	sexually mature and	discolouration of treated skin)	
	post-coitum	mated female Sprague		
		Dawley Crl:CD	<u>600 mg/kg bw/day:</u>	
		(SD)BR rats (8-12	-clinical signs (encrusted skin,	
		weeks old) received	coloured urine)	
		Quinoclamine by	↓ <b>bw loss</b> (Days 6-9: -0.41 g)	
		dermal application at	↓ <b>bw gain</b> (Days 6-16: 31%)	
		dose levels of 5, 100	↓FC	
		and 600 mg/kg	-macroscopical changes (reddish	
		bw/day for 10	discolouration of treated skin)	
		consecutive days from		
		day 6 to 15 post-	No embryotoxicity or	
		<i>coitum</i> , inclusive.	teratogenicity was noted in this	
			study	
			NOAEL maternal: 100 mg/kg	
			bw/day	
			NOAEL teratogenic effects: 600	
			mg/kg bw/day	
			The study is acceptable as	
			supplementary data.	

# Table 2.6.6.2-3. Summary table of other studies relevant for developmental toxicity

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

This section is presented by two teratology studies in the rat and two teratology studies in the rabbit. In addition the results of range finding studies (two studies for each species) to the main studies are given in the Table 2.6.6.2-1. Furthermore, a supplementary study is available conducted in the rat by the dermal route (Table 2.6.6.2-3). All studies were conducted in accordance with the OECD Principles of Good Laboratory Practice.

#### Short summary on provided information

#### Rat:

In the first teratology study in the rat, the highest applied dose was 75 mg/kg bw/day. Treatment was associated with reduced bodyweight gain (25%) and food consumption noted in dams at 75 mg/kg bw/day, changes in gross pathology (enlarged spleen) noted in dams at  $\geq$ 20 mg/kg bw/day, reduced foetal weight (7%) noted at 75 mg/kg bw/day and increased incidence of aortic abnormalities and skeletal variations noted at  $\geq$ 20 mg/kg bw/day and situs inversus and interrupt aortic arch noted at 75 mg/kg bw/day. The increased incidence of skeletal variants included effects on skull (hyoid not ossified) and vertebrae (thoracic centre one or more bilobed) noted at  $\geq$ 20 mg/kg bw/day at at 75 mg/kg bw/day and effects on sternebrae (5th and 6th not ossified; one or more bilobed, bipartite or misaligned) noted at 75 mg/kg bw/day. The NOAEL for maternal toxicity was 5 mg/kg bw/day based on reduced bodyweight gain (25%) noted in dams at 75 mg/kg bw/day and changes in gross pathology (enlarged spleen) noted in dams at  $\geq$ 20 mg/kg bw/day. NOAEL for developmental toxicity was 5 mg/kg bw/day based on reduced foetal weight (7%) noted at 75 mg/kg bw/day and increased incidence of aortic abnormalities and skeletal variations noted at  $\geq$ 20 mg/kg bw/day. NOAEL for developmental toxicity was 5 mg/kg bw/day based on reduced foetal weight (7%) noted at 75 mg/kg bw/day and increased incidence of aortic abnormalities and skeletal variations noted at  $\geq$ 20 mg/kg bw/day. NOAEL for developmental toxicity was 5 mg/kg bw/day based on reduced foetal weight (7%) noted at 75 mg/kg bw/day and increased incidence of aortic abnormalities and skeletal variations noted at  $\geq$ 20 mg/kg bw/day (Anonymous 25, 1986, Report No.: AKJ/4/86).

In the range finding study to the above mentioned main study, dose levels up to 500 mg/kg bw/day were tested. Treatment was associated with maternal mortalities (at 500 mg/kg bw/day: one animal died, the remaining four animals were killed in extremis on days 10 or 11 of pregnancy; at 200 mg/kg bw/day: one animal died, two were killed in extremis), clinical signs noted in dams at  $\geq$ 50 mg/kg bw/day (at 500 mg/kg bw/day: lethargy, hunched posture, piloerection, stained urine, soft stained faeces, stained fur around anus, vagina, head; at 200 mg/kg bw/day: lethargy, hunched posture, piloerection, stained urine, stained fur around head; at 50 mg/kg bw/day: staining around anus, vagina, head; at 80 mg/kg bw/day: stained urine, stained fur around head; at 50 mg/kg bw/day: staining around eye), maternal bodyweight loss or reduced maternal bodyweight (at 500 mg/kg bw/day: -34 g (days 7-10); at 200 mg/kg bw/day: -19.8 g (days 7-10), -1.5 g (days 10-13), 42% (n.s.) (days 13-17), at 80 mg/kg bw/day: -3.5 g (days 7-10), 14% n.s. (days 10-13)), reduced food consumption in dams noted at  $\geq$ 80 mg/kg bw/day, macroscopic changes in dams (At 200 mg/kg bw/day: enlarged spleen and adrenals, erosion of the stomach mucosa; At 80 mg/kg bw/day: enlarged spleen in one dam), increased postimplantation loss noted at 200 mg/kg bw/day, and reduced mean foetal weight noted at 200 mg/kg bw/day (27%) and 80 mg/kg bw/day (8% n.s.) (Anonymous 33, 1986, Report No.: AKJ/2/86).

In the second teratology study in the rat, the highest applied dose was 75 mg/kg bw/day. Treatment was associated with maternal clinical signs noted in dams at 20 mg/kg bw/day (paddling of the forelimbs) and 75 mg/kg bw/day (paddling of the forelimbs and nose rubbing), reduced maternal bodyweight gain noted in dams at 20 mg/kg bw/day (Days 7-8: 62%, Days 17-19: 21%) and 75 mg/kg bw/day (Days 17-19: 41%), maternal bodyweight loss noted in dams at 75 mg/kg bw/day (Days 6-7: -4.6 g, Days 7-8: -2.6 g, Days 8-9: -0.4 g), reduced food consumption noted in dams at  $\geq 20 \text{ mg/kg bw/day}$ , reduced gravid uterus weight noted at  $\geq 20 \text{ mg/kg bw/day}$ , reduced number of early intrauterine deaths noted at 75 mg/kg bw/day, reduced litter weight noted at  $\geq$ 20 mg/kg bw/day, increased post-implantations loss noted at 75 mg/kg bw/day, reduced mean litter size noted at 75 mg/kg bw/day, reduced foetal weight noted at 20 mg/kg bw/day (7%) and 75 mg/kg bw/day (12%), increased incidence of skeletal variations (incomplete ossification of skull bone (frontal and nasal) and unossified fifth sternebrae) noted at ≥20 mg/kg bw/day, and malformations noted at 75 mg/kg bw/day. The observed malformations noted at 75 mg/kg bw/day consisted of subcutaneous oedema (one animal), retro-oesophageal aortic arch (one animal), kidney misshapen (one animal), and hydropnephrosis (three animals). NOAEL for maternal toxicity was 5 mg/kg bw/day based on reduced bodyweight gain noted in dams at  $\geq 20$  mg/kg bw/day, body weight loss noted in dams at 75 mg/kg bw/day, reduced mean gravid uterus weight noted in dams at  $\geq 20$  mg/kg bw/day, reduced mean litter weight noted at  $\geq$ 20 mg/kg bw/day, increased number of pre- and post-implantation losses and early intrauterine deaths noted at 75 mg/kg bw/day, and reduced mean litter size noted at 75 mg/kg bw/day. NOAEL for developmental toxicity was 5 mg/kg bw/day based on reduced foetal weight noted at ≥20 mg/kg bw/day, increased number of post-implantation loss and early intrauterine deaths noted at 75 mg/kg bw/day, reduced mean litter size noted at 75 mg/kg bw/day, increased incidence of skeletal variations noted at  $\geq 20$  mg/kg bw/day, and malformations noted at 75 mg/kg bw/day (Anonymous 26, 2002, Report No: 619/94-D6154).

In the range finding study to the above mentioned main study, dose levels up to 100 mg/kg bw/day were tested. Treatment was associated with reduced bodyweight gain noted in dams of all treatment groups (18%, 27%, 41% in dams of 10, 50 and 100 mg/kg bw/day groups, respectively), reduced food consumption noted at  $\geq$ 50 mg/kg bw/day, reduced gravid uterus weight (17%) noted in dams at 100 mg/kg bw/day, increased post-implantation loss noted at  $\geq$ 50 mg/kg bw/day, increased number of intrauterine deaths noted at  $\geq$ 50 mg/kg bw/day, reduced mean litter size noted at 100 mg/kg bw/day, reduced mean litter weight noted at  $\geq$ 50 mg/kg bw/day, and reduced foetal weight noted at all dose levels (8%, 11%, 12% in foetus of 10, 50 and 100 mg/kg bw/day groups, respectively) (Anonymous 34, 2002, Report No.: 619/123-D6154).

In the supplementary study, rats received Quinoclamine by the dermal route at dose levels up to 600 mg/kg bw/day. Treatment was associated with maternal toxicity consisted of clinical signs (coloured urine noted at  $\geq$ 5 mg/kg bw/day and encrusted skin noted at  $\geq$ 100 mg/kg bw/day), reduced bodyweight growth noted at 600 mg/kg bw/day (bodyweight loss: -0.41 g, reduced bodyweight gain Days 6-16: 31%), reduced food consumption, and macroscopical changes (reddish discolouration of treated skin). No embryotoxicity or teratogenicity were noted in this study. The maternal NOAEL was 100 mg/kg bw/day, and the NOAEL for teratogenic effects was 600 mg/kg bw/day (Anonymous 30, 1996, Report No.: 1312-1416-001).

#### Rabbit:

In the first teratology study in the rabbit, the highest applied dose was 22.5 mg/kg bw/day. Treatment was associated with maternal reduced bodyweight gain (5%) noted at 22.5 mg/kg bw/day, reduced foetal weight noted at 22.5 mg/kg bw/day (5%. n.s.), increased incidence of skeletal variants (increased number of caudal centra  $\leq$ 15) noted at 22.5 mg/kg bw/day, and malformations noted at 22.5 mg/kg bw/day. The malformations noted at 22.5 mg/kg bw/day included scoliosis (one animal), spina-bifida (three animals), anomalies of the aortic arch (two animals), sternebral fusions (three animals) and hyperextension of limb or paw (one animal). NOAEL for maternal toxicity was 22.5 mg/kg bw/day (highest dose level). NOAEL for developmental toxicity was 7.5 mg/kg bw/day based on increased foetal variations (increased number of caudal centra  $\leq$ 15) noted at 22.5 mg/kg bw/day, and malformations 27, 1986, Report No.: AKJ/3/86).

In the range finding study to the above mentioned main study, dose levels up to 500 mg/kg bw/day were initially tested. Because of severe toxicity elicited at the highest dose level, doses were reduced after one dose to 8, 20 or 50 mg/kg bw/day. Because mating was staggered over two days, half of the animals in each group received one dose at the initial high dose level and on subsequent days were dosed at the lower level. The other half of the animals in each group received the lowere dose levels throughout the dosing period. Treatment was associated with maternal mortalities noted at 500/50 mg/kg bw/day (both animals died), clinical signs noted at  $\geq$ 50 mg/kg bw/day (at 50 mg/kg bw/day: coloured urine, at 80/8 mg/kg bw/day: coloured urine, at 200/20 mg/kg bw/day: coloured urine, at 500/50 mg/kg bw/day (at 50 mg/kg bw/day: af 50 mg/kg bw/day: dark coloured urine, lethargy, hunched posture), reduced maternal bodyweight gain noted at  $\geq$ 50 mg/kg bw/day: 12%), reduced food consumption noted at  $\geq$ 50 mg/kg bw/day, increased incidence of post-implantation loss noted at  $\geq$ 20 mg/kg bw/day, and malformations noted at  $\geq$ 20 mg/kg bw/day. The malformations noted at 20 mg/kg bw/day consisted of spina bifida (two animals), interrupted aortic arch major (one animal) and hindlimb left malrotated (one animal). At 50 mg/kg bw/day interrupted aortic arch major (one animal) and kidney left agenesis (one animal) were noted (Anonymous 28, 1986, Report No.: AKJ/1/86)

In the second teratology study in the rabbit, the highest applied dose was 30 mg/kg bw/day. Treatment was associated with mortality noted in one dam at 30 mg/kg bw/day, reduced maternal bodyweight/bodyweight change noted at 17.5 mg/kg bw/day (bodyweight change Days 12-15: 67% of control) and 30 mg/kg bw/day (reduced body weight Days 4-29: 7%, bodyweight change Days 4-29: 46% of control), reduced maternal food consumption noted at 30 mg/kg bw/day, reduced mean litter size noted at  $\geq 17.5$  mg/kg bw/day, increased post-implantation loss noted at 30 mg/kg bw/day, increased early and late intrauterine deaths noted at 30 mg/kg bw/day, reduced litter weight noted at 30 mg/kg bw/day, increased specific foetal variations noted at 30 mg/kg bw/day and foetal malformations noted at 17.5 mg/kg bw/day (hydronephrosis, abnormal terminal caudal verebrae) and 30 mg/kg bw/day (hydronephrosis, abnormal terminal caudal verebrae) and 30 mg/kg bw/day (hydronephrosis, abnormal terminal caudal verebrae) and 30 mg/kg bw/day (hydronephrosis, abnormal terminal caudal verebrae) and 30 mg/kg bw/day (hydronephrosis, abnormal terminal caudal verebrae) and 30 mg/kg bw/day (hydronephrosis, abnormal terminal caudal vertebrae, misshapen nasal bone, misaligned thoracic vertebral arch, absent frontal). The increased incidence of specific foetal variations consisted of: kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior fontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, and asymmetric ossification of cervical vertebral centra. NOAEL

for maternal toxicity was 5 mg/kg bw/day based on reduced bodyweight growth noted at 17.5 mg/kg bw/day (bodyweight change Days 12-15: 67% of control) and 30 mg/kg bw/day (bodyweight change Days 4-29: 46% of control), reduced mean litter size noted at  $\geq$ 17.5 mg/kg bw/day, increased post-implantation loss noted at 30 mg/kg bw/day, increased early and late intrauterine deaths noted at 30 mg/kg bw/day, and reduced litter weight noted at 30 mg/kg bw/day. NOAEL for developmental toxicity was 5 mg/kg bw/day based on reduced mean litter size noted at  $\geq$ 17.5 mg/kg bw/day, increased post-implantation loss noted at 30 mg/kg bw/day, increased early and late intrauterine deaths noted at 30 mg/kg bw/day, increased early and late intrauterine deaths noted at 30 mg/kg bw/day, reduced litter weight noted at 30 mg/kg bw/day, increased incidence of specific foetal variations noted at 30 mg/kg bw/day, and malformations noted at  $\geq$ 17.5 mg/kg bw/day (Anonymous 29, 2002, Report No.: 619/155-D6154).

In the range finding study to the above mentioned main study, dose levels up to 30 mg/kg bw/day were tested. Treatment was associated with abortion noted in one dam at 30 mg/kg bw/day, reduced maternal bodyweight gain noted in dams at 17.5 mg/kg bw/day (12%) and 30 mg/kg bw/day (10%), increased post-implantation loss and increased number of late intrauterine deaths noted at 30 mg/kg bw/day, reduced mean litter weight noted at 30 mg/kg bw/day, and reduced mean foetal weight (3%) noted at 30 mg/kg bw/day (Anonymous 35, 2002, Report No.: 619/122-D6154).

In addition, to the provided studies on developmental toxicity on Quinoclamine, the notifier has asked an independent expert to assess the teratogenicity of Quinoclamine to provide an independent opinion as to whether the Risk Phrase R63 is justified. The view of the expert was given in following document:

• Reporting Table No. 2 (10-14). Quinoclamine "Assessment of Reproductive Toxicity Studies" (2002)

The conclusion from this assessment is summarised below:

# Extract:

"In the two rat studies, oral administration of Quinoclamine (ACN Technical) at dosages of 5, 20 or 75 mg/kg/day during the period of organogenesis (and fetal growth in the Covance study) was associated with maternal toxicity (retarded body weight gain/ body weight loss and reduced food consumption) at 20 mg/kg/day (Covance study) and 75 mg/kg/day (both studies). This resulted in reduced fetal body weight and associated retarded fetal ossification at 20 mg/kg/day (Covance study) and 75 mg/kg/day (both studies). In the Covance study, where dosing started one day earlier (DG 6), there was also an increase in pre-and post-implantation loss at 75 mg/kg/day.

Considering both rat studies, the type, incidence and distribution of abnormalities/ malformations observed did not indicate that Quinoclamine was teratogenic at the dosages investigated. On the basis of these results, the NOEL (No Observed Effect Level) for Quinoclamine was 5 mg/kg/day for both the dam and embryo/fetus.

*In the two rabbit studies*, oral administration of Quinoclamine (ACN Technical) at dosages of 2.5, 7.5 or 22.5 mg/kg/day (Toxicol study) and 5.0, 17.5 or 30.0 mg/kg/day (Covance study) during the period of organogenesis (and fetal growth in the Covance study) was associated with maternal toxicity (retarded body)
weight gain/ body weight loss, reduced food consumption) at dosages of  $\geq 17.5$  mg/kg/day. This resulted in an increased incidence of post-implantation loss at 17.5 and 30 mg/kg/day in the Covance study, reduced fetal and/or litter weight at dosages of  $\geq 17.5$  mg/kg/day (both studies) and associated retarded fetal ossification at 22.5 mg/kg/day in the Toxicol study.

Considering both rabbit studies, neither the type, incidence or distribution of abnormalities/malformations observed indicated that Quinoclamine showed a specific dysmorphogenic effect at dosages up to and including those that were maternally toxic. The NOEL (No Observed Effect Level) for Quinoclamine was considered to be 5.0/7.5 mg/kg/day for both maternal and fetal parameters, in the Covance and Toxicol studies, respectively.

In conclusion, for both the rat and the rabbit oral embryo-fetal development toxicity studies, there is evidence of maternal toxicity and secondary embryo-fetal toxicity, as indicated by increased pre- and/or post-implantation loss, reduced fetal body weights and retarded fetal ossification in both rats and rabbits. However, for both species, the type, incidence and distribution of abnormalities/malformations were considered not to indicate a teratogenic potential for Quinoclamine when administered to pregnant animals during the period of organogenesis (and fetal growth). This conclusion is in agreement with that in the Assessment for Teratogenicity with ACN written by Anonymous 36 in 1989 based on the rat and rabbit studies performed at Toxicol in 1986 and indicates that the Risk Phrase R63 is not justified."

An assessment of reproduction toxicity conducted by the applicant (Anonymous 36, 1989) is reported in Vol. 3, section B.6.6.2.3. In this assessment malformations as found in the teratogenicity studies in rats and rabbits of Anonymous 25 (Report No.: AKJ/4/86, Report No.: AKJ73/86, Report No.: AKJ/1A/89) were viewed. Furthermore the

2-generation study by Anonymous 19 (Report No.: 854-111) were considered. The conclusion from this assessment is summarised below (for details see Vol. 3, B.6.6.2.3):

"Retardation of foetal development involving retardation of ossification was induced with quinoclamine at a dose level showing maternal toxicity in the rat and the rabbit, but no obvious evidence indicated that quinoclamine has a capability of developing a teratogenic effect."

## Overall relevance of the provided information on adverse effects on development (RMS):

Relevance of aortic arch malformations:

In the rat study by Anonymous 25, 1986 (Report No.: AKJ/4/86) incidences of aortic arch malformations were noted at the dose levels of 20 mg/kg bw/day (innominate artery absent) and 75 mg/kg bw/day (innominate artery absent, situs inversus and interrupt aortic arch). The incidence of situs inversus (mean% foetus: 0.8%) was outside historical control data for the laboratory in question (mean % foetus: 0.4%) (Table 2.6.6.2.1-1) while the defects innominate artery absent and interrupted aortic arch were not presented in historical control data for the study

performing laboratory in 1985. Additional historical control data are available for other laboratories than the study-performing laboratory for time points several years later (Table 2.6.6.2.1-2 to 4). These historical control data show that the effects on aorta arch can occur in controls. The opinion of RMS is however that it is not accurate to compare the study performed in 1986 with control data produced by another than the study-performing laboratory. Furthermore, it is not accurate to consider historical control data several years later compared to the time point of the study. According to OECD TG No. 43 (guidance document on mammalian reproductive toxicity testing and assessment)  $\pm 2$  years are recommended for historical control data as a reasonable amount of time prior to the study being interpreted in order to avoid genetic drift in the laboratory animal population.

In the rat study by Anonymous 26, 2002 (Report No.: 619/94-D6154) a single incidence of "interrupted aortic arch" occurred in the low dose group (incidence: 0.3%). No data for interrupted aortic arch were presented in the historical control data submitted by applicant for the laboratory in question (consisted of 6 studies preceding the rat study by Anonymous 26, but study year not specified) (Table 2.6.6.2.1-5). The incidence of interrupted aortic arch was however considered as incidental in this study since it occurred at a low frequency in the low dose group only.

In the rabbit study by Anonymous 27 (Report No.: AKJ/3/86) aortic arch abnormality was noted in two high dose foetuses (1.7%) (Table 2.6.6.2.1-6). Historical control data for the laboratory in question in 1985, shows that the incidence of aortic arch abnormality was within historical control value (2.2%) (Table 2.6.6.2.1-7). Aortic arch abnormality (interrupted aortic arch) was also noted in the range finding study (Report No.: AKJ/1A/86) to the main study of Anonymous 27 at the dose level of 20 mg/kg bw/day (one foetus) and 50 mg/kg bw/day (one foetus) (Table 2.6.6.2.1-8).

1 abit 2.0.0.2.1 1. 11	clucifices w	the ability at the	manormations	- Tai study of A	(Report 10.: AIS/4/00)
Symptoms	Malform 25 1986	ations in Quinc	clamine study A	anonymous	Range of group means % in background data of the laboratory in 1985
	Control	5 mg/kg bw/day	20 mg/kg bw/day	75 mg/kg bw/day	
Litters: Foetuses:	21 273	20 285	21 273	21 263	167 2171
Innominate artery absent	0	0	1 (0.4 %)	4 (1.8 %)	
Interrupted aortic arch	0	0	0	1 (0.3 %)	
Situs inversus	0	0	0	2 (0.8 %)	0 – 0.4 %

## Table 2.6.6.2.1-1: Incidences with aortic arch malformations - rat study of Anonymous 25, 1986 (Report No.: AKJ/4/86)

--= malformation not included in the background data report

i studies					
Symptoms	Malformati 1986	onymous 25	Historical control data compiled by MARTA 1989-		
	Control	5 mg/kg bw/day	20 mg/kg bw/day	75 mg/kg bw/day	1992
Litters:	21	20	21	21	4698
Foetuses:	273	285	273	263	37868
					Total studies: 223
Innominate artery absent	0	0	1	4	3.39% (max foetal incidence)
			(0.4 %)	(1.8 %)	18.18% (max litter incidence)
Interrupted aortic arch	0	0	0	1	0.45% (max foetal incidence)
-				(0.3 %)	6.25% (max litter incidence)
Situs inversus	0	0	0	2	0.86 % (max foetal
				(0.8 %)	incidence)
					4.56% (max litter incidence)

## Table 2.6.6.2.1-2: Historical control data- MARTA 1989-1992. Visceral anomalies in Crl:CD(SD)BR rats. Summary of all studies

## Table 2.6.6.2.1-3: Historical control data- MARTA/MTA 1992-1994. Visceral alterations in Crl:CD(SD)BR rats. Gestation days 20 and 21

Symptoms	Malformation 1986	ns in Quinoclar	Historical control data compiled by Marta/MTA		
	Control	5 mg/kg bw/day	20 mg/kg bw/day	75 mg/kg bw/day	1992-1994
Litters:	21	20	21	21	4.935
Foetuses:	273	285	273	263	24.340
					Total studies: 229
Innominate artery absent	0	0	1	4	1.40% (max foetal)
			(0.4 %)	(1.8 %)	9.10% (max litter)
Interrupted aortic arch	0	0	0	1	0.00% (max foetal incidence)
_				(0.3 %)	0.00% (max litter incidence)
Situs inversus	0	0	0	2	2% (max foetal incidence)
				(0.8 %)	10% (litter incidence)

## Table 2.6.6.2.1-4: Background pregnancy and foetal abnormality data from developmental toxicity studies on the Sprague-Dawley rat (Crl: CD(SD) BR. Charles River (UK) Limited. June 2000 to October 2005

Symptoms	Malformati 1986	ons in Quinocla	Historical control data (range of group means %)		
	Control	5 mg/kg	20 mg/kg	75 mg/kg	Charles River (UK)
		bw/day	bw/day	bw/day	Limited 2000-2005
Litters:	21	20	21	21	458
Foetuses:	273	285	273	263	2931
Innominate artery absent	0	0	1	4	0.0-1.8%
			(0.4 %)	(1.8%)	

## Table 2.6.6.2.1-5: Incidences with aortic arch malformations - rat study of Anonymous 26 2002 (Report No.: 619/94-D6154)

Symptom	Malforma study	Malformations in Quinoclamine study			Incidences reported in 6 studies <sup>1</sup> preceding the present study					
	Control	5 mg/kg bw/day	20 mg/kg bw/day	75 mg/kg bw/day	1	2	3	4	5	6
External / visceral abnormalities										
Litters:	24	24	24	24	22	22	23	23	22	23
Foetuses:	354	307	330	263	293	273	299	306	323	319
Interrupted aortic arch		1 (0.3 %)								

aortic arch (0.4%)	Retro-oesophageal aortic arch			1 (0.4 %)						
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<sup>1</sup>Year of study not specified

## Table 2.6.6.2.1-6: Incidences with aortic arch malformations - rabbit study of Anonymous 27, 1986 (Report No.: AKJ/3/86)

Symptom	Quinoclamine dose level (mg/kg bw/day)						
	0	2.5	7.5	22.5			
External/visceral abnormalities							
Aortic arch abnormality	1 (0.8%)	-	-	2 (1.7%)			

## Table 2.6.6.2.1-7: Comparison of incidences with aortic arch abnormalities noted at 22.5 mg/kg bw/day in the rabbit study of Anonymous 27, 1986 (Report No.: AKJ/3/86) and historical control data of the laboratory in 1985

IFIS-	Symptoms acc. to	Malformations in Quinoclamine	Range of group means % in background data
No.	IFIS	study at 22.5 mg/kg bw/day	of the laboratory in 1985 (mean %)
	(symptom as		
	described in study)		
External	/ visceral abnormalities	Total no. foetuses	Total no. foetuses examined*: 708
		examined*: 915	
	Aortic arch	2 (1.7 %)	0 – 2.2 % (0.5%)
	abnormality		

## Table 2.6.6.2.1-8: Incidences with aortic arch malformations - range finding rabbit study of Anonymous 28, 1986 (Report No.: AKJ/1/86)

,	0	8	20	50	80/8	200/20		
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg		
	bw/day	bw/day	bw/day	bw/day	bw/day	bw/day		
	Number of affected foetuses in the group (mean %)							
Interrupted aortic arch			1 (8.4%)	1 (8.4%)				
major								

In November 2006, Sweden proposed to classify Quinoclamine with Repr. Cat. 3, R63 at the meeting of the Technical Committee on Classification and labelling in Arona, 15-16 may 2007. The industry was invited to submit their arguments for absence of developmental effects during the Follow-Up procedure. An independent expert was asked by the applicant to provide comments. These comments are presented in following paper:

• "Comments to FU I. Follow-up to the meeting of the Technical Committee on Classification and Labelling in Arona, 15-16 May 2007"

The conclusion drawn by the independent expert regarding the aortic arch abnormalities was that these findings were not considered to be indicative of a teratogenic effect for the following reasons:

1. In the rat study of Anonymous 26, 2002 (Report No.: 619/94-D6154) at the same dosages as used in the rat study of Anonymous 25, 1986 (Report No.: AKJ/4/86) the single incidence of "interrupted aortic arch" occurred in the low dose group. This argues for a spontaneous occurrence of this finding rather than a treatment-related effect.

2. For the abnormality "interrupted aortic arch", there was both a lack of a relationship to dose and lack of reproducibility of the finding. Interrupted aortic arch was observed in one high dose foetus in the rat study of Anonymous 25, 1986 (Report No.: AKJ/4/86), and in one high dose foetus in the rabbit study of Anonymous 27 (Report No.: AKJ/3/86). This finding was observed in one low dose foetus in the rat study of Anonymous 26, 2002

(*Report No.:* 619/94-D6154) and was not observed in any foetuses in the rabbit study of Anonymous 29 (*Report No.:* 619/155-D6154) in which higher dosages were used and the dosing period was extended.

3. "Innominate artery absent" is described as an abnormality in the rat study of Anonymous 25, 1986 (Report No.: AKJ/4/86) while it is described as a variation in the rat study of Anonymous 26, 2002 (Report No.: 619/94-D6154). With the exclusion of the variation, "innominate artery absent", the overall incidence of abnormalities in the rat study of Anonymous 25, 1986 (Report No.: AKJ/4/86) would be 1, 0, 0, 3 (in three litters) foetuses in the control, 5, 20 and

75 mg/kg bw/day groups, respectively. Assessed together with the findings from the rat study of Anonymous 26, 2002 (Report No.: 619/94-D6154) there is no indication of a dose-related increase in any particular abnormality or group of related abnormalities in the two rat studies.

4. Three of the foetuses with "innominate artery absent" occurred in one litter in the rat study of Anonymous 25 1986 (Report No.: AKJ/4/86). This dam showed clear evidence of maternal toxicity – body weight loss between DG 8-9 (-8g), reduced food consumption between DG 7-10 (16.7 g compared with a control mean of 21.7 g), increased post-implantation loss and an enlarged spleen at necropsy.

### Comments (RMS):

The two main rat studies (Anonymous 25, 1986 and Anonymous 26, 2002) were comparable with the major differences being the length on the dosing period (DG 7-17 and DG 6-19 in the respective studies), and the vehicle (0.25% gum tragacanth and 1% aqueous methylcellulose in the respectively studies). The maternal effects, i.e. body weight reductions and reductions in food consumption were more marked in the rat study by Anonymous 26 (2002). This may be explained by a problem with allocation of the animals for this study. Prior to the start of the study there was a statistically significant reduction of mean body weight in all dose groups and therefore the animals located in the dose groups may have been younger than control animals (animals used in this study weighted between 189.8 and 314.4 g).

RMS agrees with the conclusion by the expert that the effects on aortic arch occurred at low incidences. On the other hand the effect of aortic arch was presented in several studies and in both species. Thus, this effect could suggests an adverse effect of treatment, although the dose response pattern was not clear. It has been argued by the expert that the observed incidences of the aortic arch abnormalities can be attributed either to spontaneously occurring abnormalities or to marked maternal toxicity in some of the dams. RMS agrees that the incidence of interrupted aortic arch noted in the rat study by Anonymous 26, 2002 (Report No.: 619/94-D6154) could be considered incidental since it occurred at a low frequency in the low dose group only. However, RMS does not agree that the findings of aortic arch malformations could be explained by maternal toxicity. It could be noted that aortic arch malformations could be found at dose levels without marked maternal toxicity.

<u>RMS conclusion</u>: Findings of aortic arch malformations were noted in both species and could not be explained by maternal toxicity. In the rabbit study by Anonymous 25 (1986) interrupted aortic arch was noted in two high dose foetuses (1.7%) at the dose level of 22.5 mg/kg bw/day. The incidence of interrupted aortic arch was within historical control data (2.2%). Incidences of interrupted aortic arch were also noted in the range finding study to the rabbit study of Anonymous 25 (1986) at the dose level of 20 mg/kg bw/day (one foetus) and 50 mg/kg bw/day

(one foetus). In the rat study of Anonymous 25 (1986) interrupted aortic arch was noted at the dose level of 75 mg/kg bw/day (one foetus). In addition, the aortic malformations situs inversus (two foetuses) and innominate artery absent (four foetuses) were noted at this dose level. Innominate artery absent was also noted in this study at the dose level of 20 mg/kg bw/day (one foetus). The incidence of situs inversus (mean% foetus: 0.8%) was outside the historical control data for the laboratory in question in 1985 (mean % foetus: 0.4%), while the defects innominate artery absent and interrupted aortic arch were not presented in this historical control data. An effect of Quinoclamine could not be excluded, although the incidence of aortic arch malformations was low and the effect was not reproducible in the study of Anonymous 26 (2002).

#### Relevance of hydronephrosis (=severe increased renal pelvis cavitation) and misshapen kidney:

In the rabbit study by Anonymous 29, 2002 (Report No.: 619/155-D6154) findings of the malformation hydronephrosis were noted at dose levels of 17.5 (one animal) and 30 mg/kg bw/day (two animals) (Table 2.6.6.2.1-9). The incidence of hydronephrosis noted in this study was dose related. No findings of hydronephrosis were presented in the historical control data in six studies preceding the present study (Table 2.6.6.2.1-10).

Additional historical control data are available for the laboratory in question (Table 2.6.6.2.1-11). These historical control data reflect cumulative defect data and the actual incidences in separate studies are not given. Furthermore, the period for the conduct of the studies is unknown. The opinion of RMS is that it is not accurate to compare the study performed in 2002 with control data produced several years from the time point of the study. According to OECD TG No. 43 (guidance document on mammalian reproductive toxicity testing and assessment)  $\pm 2$  years are recommended for historical control data as a reasonable amount of time prior to the study being interpreted in order to avoid genetic drift in the laboratory animal population.

There were no foetuses with hydronephrosis, misshapen kidney or slight increased renal pelvis cavitation in the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86) at doses up to 22.5 mg/kg bw/day (highest dose level used in this study). At the dose level of 50 mg/kg bw/day, one single case of kidney left agenesis was found in the range finding study to this study Anonymous 28, 1986 (Report No.: AKJ/1/86).

In the rat study by Anonymous 26, 2002 (Report No.: 619/94-D6154) findings of hydronephrosis were noted at the highest dose level of 75 mg/kg bw/day (3 animals) (Table 2.6.6.2.1-12). The incidence of hydronephrosis (1.1%) was slightly outside the control range (1.0%) of the six studies preceding the present study (Table 2.6.6.2.1-13). Furthermore, a single case of misshapen kidney occurred at 75 mg/kg bw/day. No findings of misshapen kidney were presented in the historical control data.

There were no foetus with hydronephrosis, misshapen kidney or slight increased renal pelvis cavitation in the rat study by Anonymous 27, 1986 (Report No.: AKJ/3/86) at doses up to 75 mg/kg bw/day.

## Table 2.6.6.2.1-9: Incidences with hydronephrosis - rabbit study by Anonymous 29, 2002 (Report No.: 619/155-D6154)

	Control	5 mg/kg	17.5 mg/kg	30 mg/kg			
		bw/day	bw/day	bw/day			
	Incidence (mean % foetuses)						
	Number of litters affected						
Kidney, cavitation increased, severe			1 (0.8)	2 (1.6)			
(hydronephrosis)			1	2			
Variation: increased renal pelvic cavitation	1 (0.3)	3 (1.6)	6 (4.4)	11 (8.8)			
	1	2	3	6*			

\* p<0.05

# Table 2.6.6.2.1-10: Comparison of incidences with hydronephrosis in rabbit study by Anonymous 29, 2002 (Report No.: 619/155-D6154) and historical control data of the laboratory

External / visceral abnormalities											
Symptom as described in study	Malforma	Malformations in Quinoclamine study Inc					Incidences reported in 6 studies <sup>1</sup>				
**Symptom as described in		prece					ceding the present study				
background data	Control	5	17.5	30	1	2	3	4	5	6	
		mg/kg	mg/kg	mg/kg							
		bw/day	bw/day	bw/day							
Litters:	21	18	19	16	20	21	21	21	20	20	
Foetuses:	200	176	160	124	181	188	193	183	186	193	
Hydronephrosis	-	-	1	2	-	-	-	-	-	-	

<sup>1</sup>Year of study not specified

## Table 2.6.6.2.1-11: Hydronephrosis in rabbits - Cumulative defect data in the historical background data of the laboratory $^{\rm 1}$

Symptom	Cumulative defect data in historical background data of laboratory <sup>1</sup>						
	Control group	Inactive group	Combined control & inactive				
			group				
Litters:							
Foetuses:	Number and	Number and	Number and %				
	%	%					
Increased renal pelvis cavitation	5 (0.12%)	4 (0.05%)	9 (0.08%)				
(bilateral)							
Increased renal pelvis cavition	3 (0.07%)	16 (0.21%)	19 (0.16%)				
(unilateral)							

<sup>1</sup> Incidences for individual studies not reported. Period for the conduct of studies not specified

Table 2.6.6.2.1-12:	Incidences	of foetuses	(litters)	with	hydronephrosis,	misshapen	kidney	and	increased	real	pelvic
dilation - rat study	by Anonyme	ous 26 (Rep	ort No.: 6	519/94	4-D6154)						

Symptom	Malformations in Quinoclamine						
	study						
	Control	5 mg/kg bw/day	20 mg/kg bw/day	75 mg/kg bw/day			
Hydronephrosis (uni/bilateral)				3 (1.1 %) (2)			
Variation: increased renal pelvic cavitation	21 (11)	10(7)	10 (6)	8 (8)			
	5.9%	3.4%	2.9%	3.3%			
Abnormality + variation combined	21(11)	10 (7)	10 (6)	11 (9)			
Kidney misshapen				1 (1) 0.4%			

Table 2.6.6.2.1-13: Comparison of incidences with hydronephrosis in the rat study of Anonymous 26 (Report No.: 619/9	94-
D6154) and control group values from six preceding embryo-foetal studies	

Symptom	Malformations in Quinoclamine study			Incidences reported in 6 studies <sup>1</sup> preceding the present study						
	Control	5 mg/kg bw/day	20 mg/kg bw/day	75 mg/kg bw/day	1	2	3	4	5	6
Hydronephrosis (uni/bilateral)				3 (1.1 %) 2	3 (1.0 %)		1 (0.3 %)			1 (0.3 %)
Variation: increased renal pelvic cavitation	21 (5.9%) 11	10 (3.4%) 7	10 (2.9%) 6	8 (3.3%) 8						
Kidney misshapen				1 (0.4 %)						

<sup>1</sup>Year of study not specified

For the follow-up to the meeting of the Technical Committee on Classification and Labelling in Arona, 15-16 May 2007, comments on the defect hydronephrosis were provided by an independent expert (document in dossier: "Comments to FU I. Follow-up to the meeting of the Technical Committee on Classification and Labelling in Arona, 15-16 May 2007"). Regarding the malformations hydronephrosis and misshapen kidney the conclusion by the independent expert was that these effects were not considered to be indicative of a teratogenic effect for the following reasons:

• If hydronephrosis had been due to a teratogenic effect of Quinoclamine, it would be expected that this finding would be observed in repeat studies performed at similar dosages in the same strain of both rats and rabbits. There was a low incidence of hydronephrosis in both the rat and rabbit studies in the studies performed by Anonymous 26/29, but there were no foetuses with hydronephrosis in either the rat or the rabbit study performed by Anonymous 25/27.

• There was a genetic predisposition for hydronephrosis (=severe increased renal pelvic cavitation) in the rat strain used in the rat study by Anonymous 26 -one of the control dams had severe increased renal pelvic cavitation.

• In the studies of Anonymous 26/29 marked maternal toxicity was observed in the two high dose rat dams with foetuses with misshapen kidney and/or hydronephrosis and in one of the high dose rabbit dams with a foetus with hydronephrosis (Tables below)

Observation	Control	75 mg/kg bw/day			
	mean values	Mean values	Dam no. 87	Dam no. 92	
Clinical signs:					
Paddling (immediately after dosing)	Not observed in any control animal	Observed in all 24 animals	DG 12-19	DG 11-19	
Nose rubbing (immediately after dosing)		Observed in all 24 animals	DG 13-19	DG 12-19	
Red discharge – uro-genital area		Only observed in one female	DG 14	-	
Body weight change: DG 6-9	+ 14.9 g	-7.5 g	-16.5 g	-22.8 g	
Corrected bodyweight change (DG 6-20)	+13.8%	+6.8%	-1.5%	-1.5%- 2.7%	
Food consumption: DG 7-8	27.7 g	15.5 g	15.2 g	9.4 g	
Food consumption: DG 8-9	28.8 g	18.9 g	13.0 g	9.1 g	
Litter parameters:					
Hydronephrosis (bilateral)			Foetus R6	-	

 Table 1: Rat study by Anonymous 26 (Report No.: 619/94-D6154)

Hudronenbrosis (unilateral)	Fostus P8 Fostus P1
Hyaronephrosis (unitateral)	roetus ko roetus ki
Kidney misshapen	- Foetus R3
	Only litter
	in study
	with 3 late
	resorptions

## Table 2: Rabbit study by Anonymous 29 (Report No.: 619/155-D6154)

Observation	Control Mean values	17.5 mg/kg bi	w/day	30.0 mg/kg bw/day			
		Mean	Dam no. 52	Mean	Dam no. 81	Dam	
		values		values		no. 91	
Bodyweight change	+200 g	+130 g	+50 g	- 10 g	- 250 g	+50 g	
DG 7-19							
% bw change:	- 4.3	-7.0	- 12.0	- 9.1	0.0	- 9.1	
DG 7-29							
(corrected)							
Food consumption (g/day)							
DG 7-8	128	162	167	132	0	118	
DG 8-9	131	158	139	130	4	116	
DG 9-12	137	150	144	110	1	91	
DG 12-15	138	127	144	75	0	29	
Litter parameters:							
Hydronephrosis			R4		R6	R5	
(unilateral)					High post-		
					implantation		
					loss - 6 late		
					resorptions		

## Comments (RMS):

The two main rabbit studies, Anonymous 27 (1986) and (Anonymous 29 2002), were partly comparable, with the major differences being the length of dosing (DG 6-18 and DG 7-28 in the respective studies), the vehicle (0.25% gum tragacanth and 1% aqueous methylcellulose in the respectively studies), and slightly higher doses in the rabbit study by Anonymous 29 (up to 30 mg/kg bw/day) compared to the dose levels used in the rabbit study by Anonymous 27 (up to 22.5 mg/kg bw/day). Maternal effects, i.e. body weight reductions were more marked in the Anonymous 29 study, which might be explained by the mentioned differences in study design.

Findings of hydronephrosis were noted in the rabbit study by Anonymous 29 at 17.5 mg/kg bw/day (one foetus) and 30 mg/kg bw/day (two foetuses). The effect was dose related and no findings of hydronephrosis were presented in the historical control data for

6 studies preceding the present study. Furthermore, a dose related incidence in the variation of "increased pelvic dilation" were noted in this study that was statistically significant in the high dose group. Findings of hydronephrosis were also noted in the rat study by Anonymous 29 (2002) at the highest dose level of 75 mg/kg bw/day (three foetuses). The incidence of this effect (1.1%) was slightly outside the historical control range of the 6 preceding studies (1.0%). Furthermore, a single case of misshapen kidney occurred in this study at 75 mg/kg bw/day, while no findings of misshapen kidney were present in the historical control data.

No findings of hydronephrosis were observed in the rabbit study of Anonymous 27 (1986). However, it could be noted that the highest dose level used in this study was lower than in the study of Anonymous 29 (2002). Furthermore, the length of dosing in the rabbit study of Anonymous 27 (1986) was shorter compared to the rabbit study of Anonymous 29 (2002).

<u>RMS conclusion</u>: The incidences of hydronephrosis observed in the rat and rabbit were outside the historical control range. The defect hydronephrosis observed in both sexes, the increased incidence of the variation increased pelvic dilation observed at high dose level in the rabbit study by Anonymous 29 (2002), and the single case of misshapen kidney also observed in the rabbit study of Anonymous 29 (2002), could suggest an adverse effect of treatment, also taking into account that the kidney is a target organ for Quinoclamine.

# Relevance of abnormal terminal caudal vertebrae, misshapen nasal bone, absent frontal, and misaligned thoracic vertebral arch noted in rabbits

In the rabbit study by Anonymous 29, 2002 (Report No.: 619/155-D6154) increased incidence of abnormal terminal caudal vertebrae, misshapen nasal bone and absent frontal were reported. These effects were classified as variations by the study author (Table 2.6.6.2.1-14).

Increased incidence of abnormal terminal caudal vertebrae was noted in the rabbit study by Anonymous 29 (2002) at 17.5 mg/kg bw/day (mean % foetuses: 5.6% compared to 2.3% in control) and 30 mg/kg bw/day (mean % foetuses: 6.4% compared to 2.3% in control) (Table 2.6.6.2.1-15). This effect was classified as a variation by the study author but consisted findings such as fused and absent caudal vertebrae and was therefore considered severe by the RMS. This effect was not present as a variant in the historical control data in six preceding studies. The defect misaligned, connected or absent caudal vertebra was however present as malformation in these historical control data showing low incidences (mean % foetuses: 0-1%) (Table 2.6.6.2.1-11). Maternal toxicity was present at the dose levels of  $\geq$ 17.5 mg/kg bw/day. At 17.5 mg/kg bw/ reduced maternal bodyweight change (67% of control at days 12-15) was noted. The malformation abnormal terminal caudal vertebrae could however not be explained by maternal toxicity.

Misshapen nasal bone (incidence mean% foetuses: 8.0% compared) and absent frontal (incidence mean % foetuses: 8.9%) were noted at the highest dose level in the rabbit study by Anonymous 29 (2002) (Table 2.6.6.2.1-14). These effects were not present in the historical control data in six preceding studies. Additional historical control data from the laboratory is available for the defect misshapen nasal bone showing low incidence (0.59%) (Table 2.6.6.2.1-12). These historical control data reflect cumulative defect data and the actual incidences in separate studies are not given. Furthermore, the period for the conduct of the studies is unknown. The opinion of RMS is that it is not accurate to compare the study performed in 2002 with control data produced several years from the time point of the study. According to OECD TG No. 43 (guidance document on mammalian reproductive toxicity testing and assessment)  $\pm 2$  years are recommended for historical control data as a reasonable amount of time prior to the study being interpreted in order to avoid genetic drift in the laboratory animal population.

Misaligned thoracic vertebral arch (one foetuses) was noted at the highest dose level (30 mg/kg bw/day) in the rabbit study by Anonymous 29 (2002) (Table 2.6.6.2.1-15). This malformation was not present in historical control data in six preceding studies. Although the incidence in the study was low, an effect of Quinoclamine could not be excluded. The effect was not noted in the rabbit study by Anonymous 27 (1986), but it could be noted that the highest dose level used in this study (22.5 mg/kg bw/day) was less when compared to the study by Anonymous 29 (2002) (30 mg/kg bw/day).

<u>Conclusion by RMS:</u> Increased incidence of abnormal terminal caudal vertebrae and incidences of misshapen nasal bone, absent frontal, and misaligned thoracic vertebral arch were reported in the rabbit study of Anonymous 29 (2002). These effects were not reported in the study of Anonymous 27 (1986). However, it could be noted that these studies were not fully comparable, with the major differences being the length of dosing (Anonymous 27 study: DG 6-18; Anonymous 29 study: 7-28) and slightly higher doses in the study by Anonymous 29 (up to 30 mg/kg bw/day) compared to the dose levels used in the

study by Anonymous 27 (up to 22.5 mg/kg bw/day). It could be noted that maternal toxicity was more marked in the study of Anonymous 29 (2002) compared to the maternal toxicity in the Anonymous 27 study (1986).

In the study of Anonymous 29 (2002), the incidences of abnormal terminal caudal vertebrae noted at 17.5 mg/kg bw/day (mean % foetuses: 5.6% compared to 2.3% in control) and 30 mg/kg bw/day (mean % foetuses: 6.4% compared to 2.3% in control) were considered severe by RMS, and were outside range of historical control data (mean % foetuses: 0-1%), and could not be explained by maternal toxicity. Furthermore, the findings of misshapen nasal bone (incidence mean% foetuses: 8%) and absent frontal (incidence mean % foetuses: 8.9%) and misaligned thoracic vertebral arch (one foetus) noted at the highest dose level (30 mg/kg bw/day) were considered severe by RMS, and were not presented in historical control data in the six preceding studies. An effect of Quinoclamine could not be excluded, although the incidences were low.

Table 2.6.6.2.1-14: Rabbit study by Anonymous 29, 2002 (Report No. 619/155-D6154): Defects classified as foetal variations by study author

	Control	5 mg/kg bw/day	17.5 mg/kg bw/day	30 mg/kg bw/day	Statistics			
	Incidence (mean	Incidence (mean % foetuses)						
	Number of litter	Number of litters affected						
Kidney, cavitation increased, severe (hydronephrosis)			1 (0.8) 1	2 (1.6) 2	DR*F+			
Kidney, cavitation increased, slight	1 (0.3) 1	3 (1.6) 2	6 (4.4) 3	11 (8.8) 6*	F+			
Liver, additional lobe	1 (0.4) 1	3 (1.8) 3	6 (3.5) 4	6 (4.4) 5*	F+			
Thymus, cervical remnant	10 (5.4) 5	15 (8.9) 8	19 (11.8) 10	16 (17.9) 9*	F+			
Skull, anterior fontanelle, lengthened	1 (0.8) 1		1 (1.8) 1	5 (7.9) 5*	F+			
Skull, frontal, absent				5 (8.9) 4*	F+			
Skull, maxilla, ossification incomplete		3 (2.4) 1	2 (2.4) 2	4 (6.7) 3	DR*F+			
Skull, nasal, misshapen				5 (8.0) 3	DR**F+			
Skull, aquamosal, misshapen	1 (0.6) 1		1 (1.1) 1	3 (5.6) 3	F+			
Sterneabrae, fused slight		4 (2.3) 3	5 (3.2) 2	6 (4.4) 5*	F+			
Vertebral- terminal, misshapen/misaligned/fused/absent	5 (2.3) 3	2 (1.59 2	9 (5.6) 6	9 (6.4) 7	DR*F+			
Vertebral-cervical centrum, ossification asymmetric		1 (0.8) 1	2 (1.2) 2	3 (2.7) 3	DR*F+			

Table 2.6.6.2.1-15: Comparison of abnormalities in the Quinoclamine study and number of abnormalities reported in the
historical control data of the laboratory (as summarised in addendum to DAR)

Skeletal abnormalities										
Symptom as described	Malforma	Malformations in Quinoclamine study				Incidences reported in 6 studies preceding the				
in study				_	present study					
**Symptom as	Control	5 mg/kg	17.5	30 mg/kg	1	2	3	4	5	6
described in		bw/day	mg/kg	bw/day						
background data			bw/day							
Litters:	21	18	19	16	20	21	21	21	20	20
Foetuses:	200	176	160	124	181	188	193	183	186	193
Vertebra					<u>.</u>					
Fused thoracic vertebral arch(es)	1	1	1					1		

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Symptom as described in studyMalformations in Quinoclamine studyIncidences reported in 6 studies preceding present study**Symptom as described in background dataControl5 mg/kg bw/day17.5 mg/kg bw/day30 mg/kg bw/day123456Litters:21181916202121212020Foetuses:200176160124181188193183186193Small vertebral arch(es) **Thoracic vertebral arch reduced in size1Thoracic vertebral arch absent1Additional thoracic vertebral arch **Additional thoraco- lumbar vertebral arch11Misaligned thoracicMisaligned thoracicMisaligned thoracic											
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Symptom as described	Malform	ations in Qui	noclamine stu	ıdy	Incidences reported in 6 studies preceding the					
**Symptom as described in background dataControl5 mg/kg bw/day17.5 mg/kg bw/day30 mg/kg bw/day123456Litters: Foetuses:21181916202121212020Foetuses:200176160124181188193183186193Small vertebral arch(es) **Thoracic vertebral arch reduced in size1 <t< td=""><td>in study</td><td></td><td></td><td></td><td></td><td>prese</td><td>nt study</td><td>y</td><td></td><td></td><td></td></t<>	in study					prese	nt study	y			
described in background databw/daymg/kg bw/day <t< td=""><td>**Symptom as</td><td>Control</td><td>5 mg/kg</td><td>17.5</td><td>30 mg/kg</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></t<>	**Symptom as	Control	5 mg/kg	17.5	30 mg/kg	1	2	3	4	5	6
background dataombw/dayom <th< td=""><td>described in</td><td></td><td>bw/day</td><td>mg/kg</td><td>bw/day</td><td></td><td></td><td></td><td></td><td></td><td></td></th<>	described in		bw/day	mg/kg	bw/day						
Litters: $21$ $18$ $19$ $16$ $20$ $21$ $21$ $21$ $20$ $20$ Foetuses: $200$ $176$ $160$ $124$ $181$ $188$ $193$ $183$ $186$ $193$ Small vertebral arch(es)111111111111Small vertebral arch reduced in size11 <th< td=""><td>background data</td><td></td><td></td><td>bw/day</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></th<>	background data			bw/day							
Foetuses:200176160124181188193183186193Small vertebral arch(es) **Thoracic vertebral arch reduced in size1	Litters:	21	18	19	16	20	21	21	21	20	20
Small vertebral arch(es)       1 </td <td>Foetuses:</td> <td>200</td> <td>176</td> <td>160</td> <td>124</td> <td>181</td> <td>188</td> <td>193</td> <td>183</td> <td>186</td> <td>193</td>	Foetuses:	200	176	160	124	181	188	193	183	186	193
**Thoracic vertebral arch reduced in size       1       Image: Constraint of the second secon	Small vertebral arch(es)										
arch reduced in sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeThoracic vertebral arch **Additional thoraco- lumbar vertebral arch11111Misaligned thoracicImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeMisaligned thoracicImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeMisaligned thoracicImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: sizeImage: size	**Thoracic vertebral	1									
Thoracic vertebral arch absentIIIAdditional thoracic vertebral arch lumbar vertebral arch11IMisaligned thoracicIIII	arch reduced in size										
absentIIIAdditional thoracic vertebral arch lumbar vertebral arch11IMisaligned thoracicIIII	Thoracic vertebral arch						1				
Additional thoracic       1       1       1         vertebral arch       1       1       1         **Additional thoraco- lumbar vertebral arch       1       1       1         Misaligned thoracic       1       1       1       1	absent						1				
vertebral arch       1       1       1         **Additional thoraco- lumbar vertebral arch       1       1       1         Misaligned thoracic       Image: Constraint of the second seco	Additional thoracic					-					
**Additional thoraco- lumbar vertebral arch       1       1       1         Misaligned thoracic       -       -       -       -	vertebral arch	1	1								
lumbar vertebral arch     Image: Constraint of the second se	**Additional thoraco-	1	1								
Misaligned thoracic	lumbar vertebral arch										
	Misaligned thoracic										
vertebral arch	vertebral arch				1						
Thoracic vertebral	Thoracic vertebral				1						
arch(es) malformed	arch(es) malformed										
Fused thoracic	Fused thoracic										
(vertebral) centra	(vertebral) centra	2				1			1	2	1
**Thoracic vertebral <sup>2</sup>	**Thoracic vertebral	2				1			1	2	1
centra fused	centra fused										
Hemicentric thoracic	Hemicentric thoracic										
centrum	centrum			2							
**Thoracic vertebral	**Thoracic vertebral			2							
centrum hemicentric	centrum hemicentric										
Thoracic hemivertebra	Thoracic hemivertebra	1									
		1									
Additional thoracic	Additional thoracic										
hemivertebra 1 2	hemivertebra				1					2	
Absent cervical	Absent cervical										
vertebra 1	vertebra	1									
Fused caudal vertebra.	Fused caudal vertebra				1					_	
Cleft (caudal) vertebra	Cleft (caudal) vertebra									2	
**Caudal vertebra(e) 1 2 (Mean %	**Caudal vertebra(e)		1	2				1		(Mean %	
(distal) misaligned.	(distal) misaligned.		-	_						foetal:	
connected or absent 1%)	connected or absent									1%)	

## Table 2.6.6.2.1-16: Cumulative defect data- rabbit. Foetal defect data of the laboratory<sup>1</sup>

Symptom	Cumulative defect data in historical background data of laboratory <sup>1</sup>							
	Control group	Inactive group	Combined control & inactive					
			group					
Number of foetuses examined	4233	7743	11976					
Foetuses:	Number and %	Number and %	Number and %					
Increased renal pelvis cavitation (bilateral)	5 (0.12%)	4 (0.05%)	9 (0.08%)					
Increased renal pelvis cavitation (unilateral)	3 (0.07%)	16 (0.21%)	19 (0.16%)					
Additional liver lobe	1 (0.02%)	3 (0.04%)	4 (0.03%)					
Cervical remnant of the thymus	-	-	-					
Lengthened anterior fontanelle	-	-	-					
Misshapen nasal bone	13 (0.59)	5 (0.12)	18 (0.29)					
Incomplete ossification of the frontal bones	304 (13.83%)	368 (9.04%)	672 (10.72%)					
Incomplete ossification of the maxilla bones	9 (0.41%)	2 (0.05%)	11 (0.18%)					
Fusion of the sternebrae	137 (3.24%)	217 (2.80%)	354 (2.96%)					
Caudal vertebra (distal) misaligned. Connected or	68 (1.61%)	117 (1.51%)	185 (1.54%)					
absent								
Cervical vertebral centra incompletely ossified	11 (0.26%)	18 (0.23%)	29 (0.24%)					

Asymmetric ossification of cervical vertebral centra - -

<sup>1</sup> Incidences for individual studies not reported. Period for the conduct of studies not specified

### Relevance of subcutaneous oedema and retro-oesophageal aortic arch

In the rat study by Anonymous 26, 2002 (Report No.: 619/94-D6154) the malformations severe subcutaneous oedema and retro-oesophageal aortic arch were noted in one animal each at the highest dose level (75 mg/kg bw/day). These malformations were not reported in historical control data in six studies preceding the present study (Table B.6.6.2.1-13). Comparison with incidences reported in additional historical background data of the laboratory (Table B.6.6.2.1-18) showed that these malformation could occur in control animals but the incidences were low. The opinion of RMS is however, that it is not accurate to compare the study performed in 2002 with control data produced several years from the time point of the study. According to OECD TG No. 43 (guidance document on mammalian reproductive toxicity testing and assessment) ±2 years are recommended for historical control data as a reasonable amount of time prior to the study being interpreted in order to avoid genetic drift in the laboratory animal population. Maternal toxicity was noted in the rat study by Anonymous 26 (2002). At the dose level of 75 mg/kg bw/day maternal reduced bodyweight gain (Days 17-19: 41%), body weight loss (Days 6-7: -4.6 g, Days 7-8: -2.6 g, Days 8-9: -0.4 g) and reduced food consumption was noted. The maternal toxicity could however not explain the malformations.

<u>Conclusion by RMS</u>: An effect of Quinoclamine could not be excluded, although the incidences of subcutaneous oedema and retro-oesophageal aortic arch were low.

Quinociannic study an	Quinoclamme study and control group values from six preceding emoryo focus studies (supplied after December 1995)											
Symptom	Malform	ations in Quin	oclamine		Incide	ences re	ported i	in 6 stud	lies prec	ceding		
	study				the							
					present study							
	Control	5 mg/kg	20 mg/kg	75 mg/kg	1	2	3	4	5	6		
		bw/day	bw/day	bw/day								
External / visceral abn												
Litters:	24	24	24	24	22	22	23	23	22	23		
Foetuses:	354	307	330	263	293	273	299	306	323	319		
Subcutaneous				1								
oedema				(0.4 %)								
Retro-oesophageal				1								
aortic arch				(0.4%)								

 Table 2.6.6.2.1-17: Rat study by Anonymous 26, 2002 (Report No.: 619/94-D6154). Comparison of abnormalities in the Quinoclamine study and control group values from six preceding embryo-foetal studies (supplied after December 1995)

buchgi bunu uutu bi the iubbi utbi	<b>j</b>						
Symptom as described in study Symptom as described in	Malforma	ations in Qui	inoclamine st	tudy	Incidences backgroun	s reported in lad data of the	historical laboratory*
background data	Control	5 mg/kg	20	75	Control	Inactive	Combined
C C		bw/day	mg/kg	mg/kg	group	group	control and
		-	bw/day	bw/day	0	0	inactive groups
External / visceral abnormalities						•	
Litters:	24	24	24	24			
Foetuses:	354	307	330	263	6208	11892	18100
Subcutaneous oedema				1			
(malformation)							
Subcutaneous oedema, trunk							
(variation)							
Oedema general					1	8	9
(malformation)					0	4	4
Retro-oesophageal aortic arch /							
Interrupted aortic arch, right							
subclavian artery arising from				1	1	0	1
descending aorta (may be retro-							
oesophageal)	ĺ						

## Table 2.6.6.2.1-18: Comparison of abnormalities in the Quinoclamine study and incidences reported in historical background data of the laboratory

\* Incidences for individual studies not reported. Period for the conduct of studies not specified

\*\* This symptom is classified as variation in the background data

## Relevance of hyperextension of limb or paw, spina bifida, scoliosis and sternebral fusion:

## Hyperextension of limb or paw:

Hyperextension of limb or paw was noted in all treated groups in the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86). Incidences were 2 animals (1.7%), 1 animal (0.9%) and 1 animal (0.9%) for the low-, mid- and high dose, respectively (Table 2.6.6.2.1-19). Since the hyperextension of limb or paw occurred without clear dose response pattern and was within historical control data (7.2%) (Table 2.6.6.2.1-20), the effect noted at 2.5 and 7.5 mg/kg bw/day was not considered to be treatment-related, also taken into consideration that the numbers of foetuses with major abnormalities in each group was not increased at the dose levels of 1.5 and 7.5 mg/kg bw/day (Table 2.6.6.2.1-21).

## Spina bifida:

Spina bifida was noted in the low and high dose group in the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86). The incidences were 2 and 3 animals for the low- and high dose, respectively (Table 2.6.6.2.1-19). The incidences (1.7% and 2.6% for the low and high dose, respectively) were within historical control data (8.4%). The effect noted at the low dose (2.5 mg/kg bw/day) was not considered treatment-related considering that the numbers of foetuses with major abnormalities in each group was not increased at this dose level (Table 2.6.6.2.1-21).

## Scoliosis:

Scoliosis was noted at 7.5 and 22.5 mg/kg bw/day in the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86). The incidence was one animal in each group. Since the incidence of scoliosis (0.9%) occurred without clear dose response pattern and was within historical control data (3.4%) (Table 2.6.6.2.1-20) the effect noted at 7.5 mg/kg bw/day was not considered to be treatment-related, also taken into consideration that the number of

foetuses with major abnormalities in each group was not increased at the dose level of 7.5 mg/kg bw/day (Table 2.6.6.2.1-21).

### Sternebral fusion:

Sternbral fusion was noted in three animals of the high dose group (22.5 mg/kg bw/day) in the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86). The incidence of sterebral fusion (2.6%) was outside the historical control data (0.7%) (Table 2.6.6.2.1-20).

<u>Conclusion by RMS</u>: In the rabbit study by Anonymous 27 (1986) numbers of foetuses with major abnormalities in each group was increased at 22.5 mg/kg bw/day. At the highest dose level (22.5 mg/kg bw/day) hyperextension of limb or paw (one animal) and scoliosis (one animal) was noted. Increased incidences of spina bifida (three animals) and sternebral fusion (three animals) were also noted at 22.5 mg/kg bw/day. An effect of Quinoclamine could not be excluded, although the incidences were low and with exception of the occurrence of sterebral fusion within historical control data, and these defects were not found in the rabbit study of Anonymous 29 (2002).

Table 2.6.6.2.1	-19: Incidences of hyper-	extension of limb or paw	, scoliosis, spina-bifi	da and sternebral i	fusion in the rabbit
study by Anong	ymous 27 (1986)				

Symptom	Quinoclamine dose level (mg/kg bw/day)							
	0	2.5	7.5	22.5				
Hyperextension of limb or paw	-	2 (1.7%)	1 (0.9%)	1 (0.9%)				
(Arthrogryposis bilateral) <sup>a</sup>								
Spina bifida	-	2 (1.7%)	-	3 (2.6%)				
Fused sternebrae (major fusion)	-	-	-	3 (2.6%)				
Scoliosis	-	-	1 (0.9%)	1 (0.9%)				

<sup>a</sup>Arthrogryposis has been categorized as "hyperextension of limb or paw" but may also fall under "malrotated limbs"

Table 2.6.	.6.2.1-20:	Comparison	of	abno	rmalities	in	the	Qu	inoclami	ie stud	y and	incidences	reported	in	historical
backgrour	nd data of	the laborator	·у												
	<i>a</i>							-			_				

IFIS-	Symptoms acc. to IFIS	Malformations in Quinoclamine study at	Background data of the laboratory in 1985
110.	(symptom as described in study)	22.5 mg/kg bw/uay	(range of group 76)
External /	visceral abnormalities	Total no. foetuses examined*: 915	Total no. foetuses examined*: 708
10069	Hyperextension of limb or paw (Arthrogryposis, bilateral)	1 (0.9 %)	#
10072	Malrotated limb	#	0 – 7.2 % (0.4%)
10120	Spina bifida	3 (2.6 %)	0 - 8.4 % (0.2%)
Skeletal a	bnormalities		
10614	Fused sternebra (major fusion)	3 (2.6 %)	0-0.7 % (0.1%)
10116	Scoliosis	1 (0.9 %)	0 – 3.4 % (0.8%)

\* Both controls and inactive treatments

#Arthrogryposis has been categorized as "hyperextension of limb or paw" but may also fall under "malrotated limbs".

ACN (mg/kg bw/day)	foetal weight (g)	No of foetuses examined	Litters examined	External / visceral abnormalities (%)		Skeletal abnorma	Skeletal abnormalities (%)		
				minor	major	minor	major		
0	37.4	127	16	1.5	2.6	24.0	1.3		
2.5	37.1	118	16	4.2	4.1	33.2	2.1		
7.5	39.2	110	16	3.9	1.3	27.5	0.6		
22.5	35.6	116	16	2.3	6.0	21.7	9.0		

Table 2.6.6.2.1-21: Rabbit study by Anonymous 27 (1986) –group mean data

## Relevance of foetus growth retardation and minor foetal variations:

In the rat study by Anonymous 25, 1986 (Report No.: AKJ/4/86) reduced foetal weight (7%) were noted at the dose level of 75 mg/kg bw/day and the incidence of minor skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite; sternebrae: 5th and 6th sternebrae not ossified, one or more bilobed, bipartite or misaligned) was increased. These findings were considered to be secondary to the maternal toxicity observed at this dose level. Maternal toxicity at this dose level consisted of reduced bodyweight gain (day 7-17: 25%) and enlarged spleen (4/24 animals). Increased incidence of skeletal variants (skull hyoid not ossified; vertebrae: thoracic centre one or more bilobed) was also noted at the dose level of 20 mg/kg bw/day. At this dose level maternal toxicity was not marked but consisted of enlarged spleen in one dam only.

In the rat study by Anonymous 34, 2002 (Report No.: 619/123-D6154) reduced foetal weight was noted at the dose level of 20 mg/kg bw/day (7%) and 75 mg/kg bw/day (12%), and the incidence of skeletal variations (incomplete ossification of skull bone and unossified fifth sternebrae) was increased at  $\geq$ 20 mg/kg bw/day. These findings were considered to be secondary to the maternal toxicity observed at these dose levels. At 20 mg/kg bw/day maternal reduced bodyweight gain (Days 7-8: 62%, Days 17-19: 21%) and reduced food consumption were noted. At

75 mg/kg bw/day maternal reduced bodyweight gain (Days 17-19: 41%), body weight loss (Days 6-7: -4.6 g, Days 7-8: -2.6 g, Days 8-9: -0.4 g) and reduced food consumption were noted.

In the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86) reduced foetal weight (5%, n.s.) was noted at the highest dose level of 22.5 mg/kg bw/day. Furthermore, increased no. of caudal centra  $\leq$ 15 (84.9% compared to 59.9% in control) was noted at this dose level. Minor maternal toxicity (reduced bodyweight gain, Days 0-28: 5%) was noted at 22.5 mg/kg bw/day. The reduced foetal weight was considered to be secondary to the maternal toxicity observed at this dose level. The finding of foetal variation (i.e. increased no. of caudal centra  $\leq$ 15) could however not be explained by maternal toxicity.

In the rabbit study by Anonymous 29, 2002 (Report No.: 619/155-D6154) reduced litter weight (24%) was noted at 30 mg/kg bw/day and the incidence of specific foetal variations was increased at this dose level. The increased incidence of specific foetal variations included: kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior frontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, and asymmetric ossification of cervical vertebral centra (Table 2.6.6.2.1-22). The findings of abnormal

terminal caudal vertebra, misshapen nasal bone and absent frontal were reported by the study author as variations (Table 2.6.6.2.1-22) but were considered as malformations by the RMS. Maternal toxicity was noted at  $\geq$ 17.5 mg/kg bw/day. Reduced maternal bodyweight change was noted at 17.5 mg/kg bw/day (Days 12-15: 67% of control) and 30 mg/kg bw/day (Days 4-29: 46% of control). In addition, reduced maternal body weight (7%) and mortality (one dam was killed on Day 18 of gestation due to severe inappetence and body weight loss and had red discharge from the urogenital region) was noted at 30 mg/kg bw/day. The finding of reduced skeletal ossification (incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebral centra) noted at the highest dose level was considered to be secondary to maternal toxicity. Historical control data from the laboratory in question is available. However, these data reflect cumulative defect data and the actual incidences in separate studies are not given. Furthermore, the period for the conduct of the studies is unknown (Table 2.6.6.2.1-23).

<u>Comments and conclusions (RMS)</u>: Reduced foetal weights were noted in both rats and rabbits at maternal toxicity dose levels. Furthermore, increased incidences of foetal variations were noted in both rats and rabbits. In the rat study by Anonymous 25 (1986) increased incidences of skeletal variations were noted at 20 mg/kg bw/day (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed) and 75 mg/kg bw/day (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite; sternebrae: 5th and 6th sternebrae not ossified, one or more bilobed, bipartite or misaligned). These effects were noted at maternal toxicity dose levels, although it could be noted that the maternal toxicity was not marked at 20 mg/kg bw/day (enlarged spleen in one dam only). Also in the rat study by Anonymous 26 (2002) increased incidences of skeletal variations (incomplete ossification of skull bone and unossified 5th sternebrae) were observed at maternal toxicity dose level of  $\geq$ 20 mg/kg bw/day.

In the rabbit study by Anonymous 27 (1986) increased incidence of caudal centra  $\leq 15$  was noted at the highest dose level of 22.5 mg/kg bw/day. This defect occurred in the absence of marked maternal toxicity. In the rabbit study of Anonymous 29 (2002) the incidences of specific foetal defects: kidney cavitation, additional liver lobe, cervical remnant of thymus, lengthened anterior frontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, and asymmetric ossification of cervical vertebral centra were increased at the highest dose level of

30 mg/kg bw/day. These defects occurred in the presence of maternal toxicity.

<u>As a conclusion</u> reduced foetal weights were noted in both species at maternal toxicity dose levels. In addition increased incidences of skeletal variations indicative of retarded foetal ossification were noted in the rat at maternal toxicity doses. In the rabbit, increased incidences of skeletal variations (increased incidence of caudal centra  $\leq 15$ ) were noted at a dose level without marked maternal toxicity. Increased incidences of specific variations (kidney caviation, additional liver lobe, cervical remnant of thymus, lengthened anterior frontanelle, incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, asymmetric ossification of cervical vertebral centra) were noted at a maternal toxicity dose.

## Table 2.6.6.2.1-22: Rabbit study by Anonymous 29, 2002 (Report No. 619/155-D6154): Foetal variations

	Control	5 mg/kg	17.5 mg/kg	30 mg/kg	Statistics
		bw/day	bw/day	bw/day	
	Incidence (me	ean % foetuses)			
	Number of lit	ters affected			
Kidney, cavitation increased,			1 (0.8)	2 (1.6)	DR*F+
severe (hydronephrosis)			1	2	
Kidney, cavitation increased, slight	1 (0.3)	3 (1.6)	6 (4.4)	11 (8.8)	F+
	1	2	3	6*	
Liver, additional lobe	1 (0.4)	3 (1.8)	6 (3.5)	6 (4.4)	F+
	1	3	4	5*	
Thymus, cervical remnant	10 (5.4)	15 (8.9)	19 (11.8)	16 (17.9)	F+
	5	8	10	9*	
Skull, anterior fontanelle,	1 (0.8)		1 (1.8)	5 (7.9)	F+
lengthened	1		1	5*	
Skull, frontal, absent				5 (8.9)	F+
				4*	
Skull, maxilla, ossification		3 (2.4)	2 (2.4)	4 (6.7)	DR*F+
incomplete		1	2	3	
Skull, nasal, misshapen				5 (8.0)	DR**F+
-				3	
Skull, aquamosal, misshapen	1 (0.6)		1 (1.1)	3 (5.6)	F+
	1		1	3	
Sterneabrae, fused slight		4 (2.3)	5 (3.2)	6 (4.4)	F+
_		3	2	5*	
Vertebral- terminal,	5 (2.3)	2 (1.59	9 (5.6)	9 (6.4)	DR*F+
misshapen/misaligned/fused/absent	3	2	6	7	
Vertebral-cervical centrum,		1 (0.8)	2 (1.2)	3 (2.7)	DR*F+
ossification asymmetric		1	2	3	

### Table 2.6.6.2.1-23: Cumulative defect data. Foetal defect data of the laboratory<sup>1</sup>

Symptom	Cumulative defe	ect data in historic	cal background data of laboratory <sup>1</sup>
	Control group	Inactive group	Combined control & inactive
			group
Number of foetuses examined	4233	7743	11976
Foetuses:	Number and	Number and	Number and %
	%	%	
Increased renal pelvis cavitation (bilateral)	5 (0.12%)	4 (0.05%)	9 (0.08%)
Increased renal pelvis cavitation (unilateral)	3 (0.07%)	16 (0.21%)	19 (0.16%)
Additional liver lobe	1 (0.02%)	3 (0.04%)	4 (0.03%)
Cervical remnant of the thymus	-	-	-
Lengthened anterior fontanelle	-	-	-
Misshapen nasal bone	13 (0.59)	5 (0.12)	18 (0.29)
Incomplete ossification of the frontal bones	304 (13.83%)	368 (9.04%)	672 (10.72%)
Incomplete ossification of the maxilla bones	9 (0.41%)	2 (0.05%)	11 (0.18%)
Fusion of the sternebrae	137 (3.24%)	217 (2.80%)	354 (2.96%)
Caudal vertebra (distal) misaligned. Connected or	68 (1.61%)	117 (1.51%)	185 (1.54%)
absent			
Cervical vertebral centra incompletely ossified	11 (0.26%)	18 (0.23%)	29 (0.24%)
Asymmetric ossification of cervical vertebral centra	-	-	-

<sup>1</sup> Incidences for individual studies not reported. Period for the conduct of studies not specified

#### Relevance of abortion/implantation loss/intrauterine death:

## Rat:

In the rat study by Anonymous 25 1986 (Report No.: AKJ/4/86) there were no abortions, and no effects of treatment at any dose level on implantation or on post-implantation losses, although it could be noted that post-implantation loss was slightly increased (not statistically significant) at the highest dose level of 75 mg/kg bw/day (7.2% compared to 6.3% in control) (Table 2.6.6.2.1-24). Maternal toxicity consisted of reduced bodyweight gain (day 7-17: 25%) and enlarged spleen (4/24 animals) noted at 75 mg/kg bw/day, and enlarged spleen (one dam only) noted at

20 mg/kg bw/day.

In the rat study by Anonymous 26, 2002 (Report No.: 619/94-D6154) there were increases in both pre- and postimplantation losses noted at the highest dose level of 75 mg/kg bw/day, which resulted in statistically significant reduced live litter size (12 compared to 14.8 in control) (Table 2.6.6.2.1-25). The incidence of post-implantation loss (11% compared to 5% in control) was not statistically significant but was higher than expected from the current background data (background data 4.0%-6.5%). The incidence of pre-implantation loss (17.4% compared to 8.6% in control) was not statistically significant and within live expected from the current background data (3.9%-24.3%). Increased number of early intrauterine deaths was also noted at 75 mg/kg bw/day (1.1 compared to 0.7 in control) but the increase was not statistically significant. The maternal effects were more marked in this study compared to the study of Anonymous 25, which might be explained by a problem with the allocation of the animals indicating that the animals at 20 and 75 mg/kg bw/day were probably younger than the allocated to the control group. Maternal toxicity was noted at  $\geq 20$  mg/kg bw/day. Reduced food consumption and maternal bodyweight gain was noted at 20 mg/kg bw/day (Days 7-8: 62%, Days 7-19: 21%) and 75 mg/kg bw/day (Days 17-19: 41%). Maternal body weight loss (Days 6-7: -4.6 g, Days 7-8: -2.6 g, Days 8-9: -0.4 g) was noted in addition at 75 mg/kg bw/day.

Dose level	Number	Mean no.	Mean no. of	Mean no.	Mean no of	Mean	Mean post-	Sex
(mg/kg/day)	pregnant/	of corpora	implantations	of live	dead	preimplantation	implantation	ratio
	number	lutea	±S.D.	foetuses	implantations	loss (%)	loss (%)	M:F
	mated	±S.D.		±S.D.	±S.D.			
Control	21/24	18.6±3.3	13.8±3.9	13.0±4.0	0.8±1.2	24.6	6.3	1.12:1
5	20/24	17.8±2.5	14.9±1.8	14.3±1.9	0.6±0.9	15.8	4.0	0.99:1
20	21/24	17.5±2.8	13.9±3.5	13.0±3.5	0.9±1.6	20.5	5.9	0.90:1
75	21/24	17.2±1.5	13.5±2.0	12.5±2.9	$1.0{\pm}1.4$	21.2	7.2	0.98:1
Analysis of		NS	NS	NS	NS			
variance								
Kruskal-						NS	NS	
Wallis test								
Chi <sup>2</sup> test								NS

Table 2.6.6.2.1-24: Rat study by Anonymous 25 (1986): Group mean pregnancy data

Table 2.6.6.2.1-25: Rat study by Anonymous 26 (2002): Group mean caesarean data

Maan intoleo (a/animal/day)	0	5	20	75
Mean make (g/ammai/day)	(mg/kg bw/da	ıy)		
Pregnant / mated females (Day 20 gestation)	24/24	22/24	24/24	22/24
No. of corpora lutea per female	16.8	15.3	16.3	16.3
No. of implantations per female	15.5	14.8	14.6	13.1**
Pre-implantation loss (%)	8.6	3.3	9.1	17.4
Early intrauterine deaths	0.7	0.8	0.8	1.1
Late intrauterine deaths	0.0	0.0	0.1	0.1
Post-implantation loss (%)	5.0	5.6	6.0	11.0
No of live foetuses per female	14.8	14.0	13.8	12.0**

## Rabbit:

In the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86) dose levels up to 22.5 mg/kg bw/day were used. Pre-implantation loss and number of implantations were comparable in all groups, and no dams aborted or showed total resorption. Post-implantation loss, live litter size were not adversely affected by treatment (Table B.6.6.2.1-26). Maternal toxicity (reduced bodyweight gain, Days 0-28: 5%) was noted at 22.5 mg/kg bw/day but was not considered adverse.

In the rabbit study by Anonymous 29, 2002 (Report No.: 619/155-D6154) dose levels up to 30 mg/kg bw/day were used. One control female and two females in each of the groups which received Quinoclamine, aborted between Gestation Days 23-28. All these females had shown a slight weight loss between DG 4-7, prior to the start of dosing on DG 7, and all showed marked inappetence from DG 4 until they aborted. In addition, there was one female at 5 mg/kg bw/day, and 2 females each at 17.5 and 30 mg/kg bw/day which showed total resorption. These females also showed marked inappetence and weight loss from DG 4. For all these animals, foetal loss was considered to be related to the inappetence, which had started prior to the start of the dosing period, and not to treatment with Quinoclamine (Table 2.6.6.2.1-27). Pregnancy rate and pre-implantation loss were comparable in

all groups. There was an apparent dose-related increase in the incidence of post-implantation loss, but at 5 mg/kg bw/day, live litter size was comparable with that of the control group. In comparison, live litter size at 17.5 mg/kg bw/day (8.4 foetuses per female compared to 9.5 in control) and 30 mg/kg bw/day (7.8 foetuses per female compared to 9.5 in control) was slightly reduced (Table 2.6.6.2.1-28). Maternal toxicity was noted at ≥17.5 mg/kg bw/day. Reduced maternal bodyweight change was noted at 17.5 mg/kg bw/day (Days 12-15: 67% of control) and 30 mg/kg bw/day (Days 4-29: 46% of control). At 30 mg/kg bw/day, reduced body weight (Days 4-29: 7%) and food consumption was noted in addition, and one dam was killed on Day 18 of gestation (due to severe inappetence and body weight loss and had red discharge from the urogenital region).

Table B.6.6.2.1-26: Rabbit stud	y by	Anonymous 27	(1986): Average	pregnancy success
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ACN	pregnant /	No. of	No. of	No of	No. of dead	Pre-impl.	Post-	Sex ratio
(mg/kg bw/day)	mated	corpora	implantations	live	implantations	loss	impl.	M:F
	females	lutea		foetuses		(%)	loss (%)	
0	16/16	13.4	9.5	7.9	1.6	28.2	17.5	1.2:1
2.5	16/16	13.1	9.9	7.4	2.5	25.1	23.6	0.8:1
7.5	16/16	11.8	8.8	6.9	1.9	23.6	22.9	1.0:1
22.5	16/16	12.2	9.3	7.3	2.0	22.4	20.8	0.7:1
Analysis of		NS	NS	NS	NS			
variance								
Kruskal-Wallis						NS	NS	
test								
Chi <sup>2</sup> test								NS

Table B.6.6.2.1-27: Rabbit study by Anonymous 29 (2002): Female performance

Number of animals	0	5	17.5	30
	(mg/kg bw/day)			
In group	24	24	24	24
Not pregnant	2	2	1	3
Pregnant / (%)	22 (91.7)	22 (91.7)	23 (95.8)	21 (87.5)
Died/killed	0	1	0	1
Aborted and killed	1	2	2	2
With total embryo/foetal loss	0	1	2	2
With live foetuses on Day 29	21	18	19	16

Mean intake (g/animal/day)	0	5	17.5	30	Statistics	
Day of gestation	(mg/kg bw/	(mg/kg bw/day)				
Pregnant / mated females (Day 29)	12/24	18/24	19/24	16/24	J	
No. of corpora lutea	11.9	13.1	11.9	11.8	J	
No. of implantations	10.1	11.4	10.1	10.2		
Pre-implantation loss (%) / No. of affected	1/1 8/1/	11.6/10	14 4/15	13 1/9	F+	
dams	14.0/14	11.0/10	14.4/15	13.17		
Early intrauterine deaths	0.2	0.9	0.7	1.0	F+	
Late intrauterine deaths	0.3	0.8	0.9	1.4	F+	
Dead foetuses. % / No. of affected dams	0.0/0	0.0/0	0.0/0	0.1/1	F+	

Post-implantation loss (%) / No. of affected dams	4.8/10	13.6/14	15.2/14	24.9/13*	F+
Mean number of foetuses per female	9.5	9.8	8.4	7.8	DR*J

Comments and conclusions:

In the rat study by Anonymous 26 (2002) increased incidence of post-implantation loss (11% compared to 5% in control) was noted at the highest dose level of 75 mg/kg bw/day. This effect was not statistically significant but the incidence was above expected background data (4.0%-6.5%). Furthermore, statistically significant reduced live litter size (12 compared to 14.8 in control) was noted at this dose level, and the number of early intrauterine deaths was increased (but not statistically significant). Maternal toxicity, such as reduced bodyweight gain (41%) and bodyweight loss, was observed at 75 mg/kg bw/day. In the study by Anonymous 25 (1986) implantation loss and live litter size were not adversely affected by treatment. However, it could be noted that the maternal effects were more marked in the study by Anonymous 26 (2002), which might be explained by a problem with the allocation of the animals indicating that younger animals were allocated in the mid- and high dose groups compared to the control group.

In the rabbit study by Anonymous 29 (2002), abortions were noted in animals of both control and treated groups, but these absortions were not considered substance related. In this study, dose related increased post-implantation loss was noted, but this effect was statistically significant only at the high dose level (30 mg/kg bw/day). At the dose level of 5 mg/kg bw/day increased post-implantation loss was observed but this effect was not statistically significant and live litter size was comparable with that of the control group. Maternal toxicity, such as mortality (one dam) and reduced bodyweight (7%), was noted at 30 mg/kg bw/day (46% of control). As a conclusion increased incidence of post-implantation loss was noted in both sexes. In addition, reduced live litter size (statistically significant) and increased number of early intrauterine deaths (not statistically significant) was noted in the rat. These effects were noted at dose levels with maternal toxicity with exception of the post-implantation loss noted in the range-finding study to rabbit study by Anonymous 27, for which no maternal toxicity was presented.

## <u>Applicant's comment on the observed effects on foetal development</u> Text below is an extract from document M-CA Section 5

"During the prior evaluation of Quinoclamine, RMS Sweden decided to propose a classification "Repro cat.3 R63 Possible risk of harm to the unborn child", based on two major findings: The effect on heart vessels and the hydronephrosis.

The applicant presents data which show these effects may not be derived from direct chemical effects of Quinoclamine but rather could also be effects triggered by transient undernutrition of the pregnant animals due to reduced food uptakein the first days of the exposur period:

After Quinoclamine treatment, both in rats and in rabbits transient reduced food consumption, body weight loss and/or reduced body weight gain were observed after initiation of Quinoclamine treatment lasting up to 10 days (corresponds approx. to gestational day 17, depending on the study type and animal species). During the subsequent dosing period, food consumption and weight gain increased again but final maternal body weight remains somewhat reduced compared to control or lower dosing groups. It is obvious that the animals were transiently in a state of undernutrition.

It is well known that maternal undernutrition can alter uterine environment dramatically and lead to significant impairment of uterine conditions. Impairment of the intrauterine growth environment during critical periods may result in perturbations of development, characterized by intrauterine growth restriction (IUGR) and low birth weight (LBW). However furthermore, maternal homocysteine levels have been described to be increased in rats as a consequence of dietary restriction (Petrie et al. 2002; Okawa et al. 2006) (KCA 5.6.2/01 & 02). Homocysteine is a non-protein amino acid which provides the methyl group for essentially all biological methylation reactions as an intermediate within the metabolism of the essential amino acid methionine including epigenetic reprogramming. Furthermore, it has been proposed that hyperhomocysteinemia can also lead to delayed effects due to induction of epigenetic changes (Krishna et al. 2013) (KCA 5.6.2/33), and there is no reason why this should not also be expected during foetal development.

Homocystein is not directly obtained from the diet but biosynthesized from nutritional methionine in a multi-step process (Blom und Smulders 2011) (KCA 5.6.2/03). It is described to be cytotoxic (Lin et al. 2014; Nakanishi et al. 2005) (KCA 5.6.2/04 & 5) and can itself be re-methylated to methionine or irreversibly trans-sulfurated to cysteine. Re-methylation to methionine depends on Vitamin B12 and requires an intact folate-cycle whose functionality itself depends amongst other factors on sufficient availability of folic acid. Trans-sulfuration to cysteine depends on sufficient Vitamin B6 supply (Blom und Smulders 2011) (KCA 5.6.2/03).

Hyperhomocysteinemia is often caused by a deficiency in vitamin availability, however, as mentioned above, is also observed in cases of maternal undernutrition or malnutrition.

The elucidation of the pathogenic mechanisms that lead to elevated homocysteine concentrations is an ongoing process. (Rees 2002) (KCA 5.6.2/06) reviewed the available information and concluded that a nutritional imbalance of S-containing amino acids in combination with low dietary protein content might be causative. Many semi-synthetic experimental diets contain an imbalance in S-containing amino acids, forcing the animal to synthesize a sizable part of its cysteine requirement from methionine. Unfortunately, when the diet is low in protein, the oxidation of amino acids is reduced, perturbing methionine metabolism and increasing levels of homocysteine. Similarly, (Li et al. 2009) (KCA 5.6.2/07) determined that hepatic methionine metabolism and therefore the homocysteine metabolism is regulated by nutritional status. The liver is a major site of methionine metabolism. In 20 h fasted mice the plasma. homocysteine levels were increased while liver methionine content was reduced. Correspondingly it was shown by gene expression analyses that several key enzymes involved in homocysteine metabolism were significantly influenced in response to starvation. Homocysteine concentrations decreased promptly when feeding was restored. Since only 20 hours of starvation were sufficient to induce an increase in plasma homocysteine levels, it can easily be assumed that the 10-day time period of undernutrition observed in rats during Quinoclamine exposure is also sufficient to do so. It is commonly accepted that maternal deficiencies in folic acid will induce severe malformations in the developing fetus, e.g. defects in the neural tube

and heart defects. Aortic arch defects in particular, were described in folic acid deficient rats by Baird et al. (1954) (KCA 5.6.2/08).

As already mentioned, an increase in maternal homocysteine concentrations was observed under protein deficiency. Homocysteine will be re-methylated under consumption of methylene tetrahydrofolate (active derivate of folic acid) and pools become depleted (James et al. 1997) (KCA 5.6.2/09). An excess of homocysteine is therefore in some ways similar to a dietary folate deficiency (Rees 2002) (KCA 5.6.2/06), which in turn may induce these heart defects.

Direct associations between hyperhomocysteinemia, folic acid deficiency and congenital heart defects in rat fetuses were described in (Lu et al. 2011) (KCA 5.6.2/10) and reviewed by (Mone et al. 2004) (KCA 5.6.2/11). It was also shown by (Nagai et al. 2001) (KCA 5.6.2/12) that homocysteine inhibits angiogenesis in bovine aortic endothelial cells, human microvessel endothelial cells and in vivo using the chorioallantoic membrane (CAM) assay.

Furthermore it was shown by Rosenquist et al. (1996) (KCA 5.6.2/13) that homocysteine directly caused heart defects in avian embryos. The authors suggested either a cytotoxic effect of homocysteine or growth factor-like effects (Tsai et al. 1994) (KCA 5.6.2/14) or even a combination of both. Early vascular development was also impaired by homocysteine in chicken embryos (Oosterbaan et al. 2012) (KCA 5.6.2/15).

Within this context, it was reported by Gerard et al. (2014) (KCA 5.6.2/16) that folic acid depleted diet administered to rats alters protein abundance in the aorta of the respective animals compared to folic acid supplemented or control rats. Most of the identified proteins are involved in cytoskeleton-related processes important to cell function/maintenance, assembly/organization, and movement. The authors concluded that expression of proteins essential to vascular structure and, presumably, function is modulated by high intake as well as deprivation of folic acid.

Van Mil et al. (2010) (KCA 5.6.2/17) extensively reviewed the associations between hyperhomocysteinemia and congenital malformations in chicken and rodent studies.

It is therefore reasonable to assume, that the aortic arch abnormalities observed in rats and rabbits were not caused by Quinoclamine treatment but by an increased homocysteine concentration triggered by severe and prolonged food avoidance of maternal animals during a critical phase of pregnancy.

Several publications describe the influence on undernutrition or malnutrition on kidney development. It was reported, that IUGR, which can be provoked by restriction in food supply, is associated with impaired kidney development in the fetus (reviewed by Vaccari et al. 2015; Lakshmy 2013, Schreuder et al. 2006; Franco et al. 2012) (KCA 5.6.2/18 & 19 & 20 & 21):

In rats, nephrogenesis begins about day 12 of gestation and is not complete until 8 days after birth. (Franco et al. 2012) (KCA 5.6.2/21). The resulting renal deficits of IUGR were manifold and the severity does not depend on the time point when undernutrition occurs during pregnancy. It was shown that developmental defects were of functional and morphological nature. Consequences of kidney damage were associated with several diseases later on in life, e.g. hypertension, impaired glucose tolerance, insulin resistance and adiposity. To date, few mechanisms are clearly identified by which kidney morphology and functionality can be affected during development under IUGR. Intrarenal Renin-Angiotensin system, renal sodium transport, apoptosis, IGF-I reduction, uric acid and nitric oxide are discussed as being potentially involved within this context, but epigenetic

impact and changes in the methylation state of DNA by associations with elevated homocysteine levels are also considered.

It is not fully clear whether hyperhomocysteinemia is also directly involved in impaired fetal kidney development. There were indications, that homocysteine induces vascular dysregulation in rat vascular smooth muscle cell functions. It is known that homocysteine dysregulates a number of vascular factors that regulate vascular smooth muscle tone and cell proliferation (Tsai et al. 1994; Qureshi et al. 2005; Iselin et al. 1998) (KCA 5.6.2/14 & 22 & 23). It has been found to impair the synthesis and bioactivity of nitric oxide (NO) (Qureshi et al. 2005; Chandler et al. 2009) (KCA 5.6.2/22 & 24). NO, originally identified as an endothelium-derived relaxing factor, is considered to be the main regulatory gaseous molecule involved in a wide range of biological processes, acting as second messenger and neurotransmitter. NO is synthesized from L-arginine via NO synthase (NOS) activation, in the presence of cofactors (reviewed in Fernandes und Hernandez 2016) (KCA 5.6.2/25). NO is known to reduce the tone of smooth muscle cells after appropriate stimulation and subsequent release (Loscalzo 2013; Furchgott und Zawadzki 1980) (KCA 5.6.2/26 & 27). The ureter is a syncytial smooth muscle that spreads its excitation electronically from cell to cell, and coordinated motility may not need an extensive neural network (Tahara 1990) (KCA 5.6.2/28).

The mechanism underlying changes in peripheral and renal vascular tone has not been fully explained. It was discussed in (Bank et al. 1994) (KCA 5.6.2/29) that since NO is synthesized continuously by endothelial cells and acts locally to modulate vascular smooth muscle tone, a reduction in its supply might in itself result in a higher setting of smooth muscle tone. Alternatively, a decrease in NO supply could allow other vasoactive substances produced by the endothelium or nerve endings or those circulating in the blood to elevate vascular smooth muscle tone. It has been proposed that the balance among vasoconstrictors versus vasodilators is important in setting vascular tone. Rather, the reduced availability of NO per se appears to cause a resetting of intrinsic vascular smooth muscle tone, presumably mediated by an increase in intracellular calcium concentration or sensitivity leading to impaired vaso-relaxation.

Iselin et al. (1998) (KCA 5.6.2/23) also demonstrated that NO may contribute to the regulation of tone of the ureters in humans. In animal models where the ureters were acutely obstructed by surgery or other manipulations, NO was found to reduce the pressure of the obstructive ureter in a dose dependent manner (Yan et al. 2012; Stief et al.1996) (KCA 5.6.2/30 & 31).

It was reviewed by Andersson und Persson (1994) (KCA 5.6.2/32) that NO influences also the lower urinary tract (urethra and urinary bladder) smooth muscles in different ways. It was, amongst others, suggested that NO may be involved in the decrease in intraurethral pressure.

An increase in the vascular tone, provoked by a homocysteine triggered NO deficit, may therefore lead to a constriction within the ureter as a tubular organ and consequently may severly constrict or even interrupt the urine flow from the kidney into the bladder. An obstruction of the free flow of urine from the kidney will lead to increased pressure within its structures. A dilatation of the renal pelvis might be the histopathological result, macroscopically termed hydronephrosis.

It was also reported that NO suppresses vascular smooth muscle cell proliferation (Tsai et al. 1994) (KCA 5.6.2/14). Its inhibition by homocysteine may therefore promote myointimal hyperplasia (Qureshi et al. 2005) (KCA 5.6.2/22). A hyperplasia of cells within the tubular ureter will presumably similarly lead to an obstruction of the ureter ending up in hydronephrosis by an interruption of urine flow and subsequent increase of renal pelvic pressure.

Hydronephrosis as a renal injury was observed after Quinoclamine treatment in rats and rabbits. According to the above presented mechanism, hydronephrosis could well be the consequence of sharply restricted dietary intake of the maternal animals rather than a direct embryotoxic effect of Quinoclamine.

Accordingly, the applicant propose no classification for Quinoclamine with respect to embryotoxicity."

### **RMS comments:**

1. RMS does not agree that the findings of aortic arch malformations could be explained by maternal malnutrition. It could be noted that aortic arch malformations could be found in the rat at dose levels without marked maternal toxicity. In the rat study by Anonymous 25 (AKJ/4/86) no effects on food consumption or bw growth were noted at the dose level of 20 mg/kg bw/day. At this dose level innominate artery absent was noted in one foetus. At the dose level of 75 mg/kg bw/day statistically significant reduced food intake was noted during days 7-10 (25%), 10-13 (14%) while the effect on food consumption during days 13-17 (4% reduction) was not statistically significant and no effects on food consumption were noted post-treatment (days 17-20). At this dose level bodyweight was reduced during days 7-17 (25%). Abnormalities observed at this dose level consisted of innominate artery absent, situs inversus and interrupt aortic arch. It is douptful that the occurrence of these abnormalities could be explained by maternal malnutrition, taking into consideration that no malnutrition was noted at the dose level of 20 mg/kg bw/day. Anomalies of the aortic arch were also noted in two animals in the rabbit study by Anonymous 27 (AKJ/3/86) at the highest dose level of 22.5 mg/kg bw/day. No effects on food consumption were noted in this study. Thus, the observed anomalies of the aortic arch could not be explained by maternal malnutrition.

Furthermore, RMS does not agree that the findings of hydronephrosis could be explained by maternal malnutrition. It could be noted that hydronephrosis could be found in the rabbit at dose levels without effects on food consumption. In the rabbit study by Anonymous 29 (Report No.: 619/155-D6154) hydronephrosis was noted in one animal at the dose level of 17.5 mg/kg bw/day. No effects on food consumption were noted at this dose level.

2. Applicant has submitted several data from the open literature to support its view that the observed developmental effects could be effects triggered by transient undernutrition of the pregnant animals. The references are listed below. No study summaries are however available, and RMS has not evaluated these data.

1.	Petrie, L., Duthie, S.J., Rees, W.D., McConnell, J.M. (2002). Serum concentrations of homocysteine are elevated
	during early pregnancy in rodent models of fetal programming
	British Journal of Nutrition 88 (5), pp. 471–477
	No GLP, published
2	Okawa H. Morita T. Sugiyama K. (2006). Increased plasma homocysteine concentration in rats from a low casein
2.	diat
	uct. Bioscience Biotechnology and Biochemistry 70 (12) pp. 2050–2053
	bioscience, biotechnology, and biochemistry 70 (12), pp. 3030–3033
2	
3.	Blom, H.J., Smulders, Y. (2011). Overview of homocysteine and folate metabolism. With special references to
	cardiovascular disease and neural tube defects.
	Journal of Inherited Metabolic Disease 34 (1), pp. 75–81
	No GLP, published
4.	Lin, N., Qin, S., Luo, S., Cui, S., Huang, G., Zhang, X. (2014). Homocysteine induces cytotoxicity and proliferation
	inhibition in neural stem cells via DNA methylation in vitro.
	The Federation of European Biochemical Societies Journal 281 (8), pp. 2088–2096
	No GLP, published
5	Nakanishi T Akabane F R Nanami M Kiyobayashi Y Moriguchi R Hasuike Y et al (2005) Comparison of
5.	Cutatoriaity of Cutatine and Homosysteina for Renal Enitheria Calls
	Violutiery of Cystellie and Homocystellie for Kenar Epinenia Cens.
	Ne chi a la l
	No GLP, published
6.	Rees, William D. (2002). Manipulating the sulfur amino acid content of the early diet and its implications for long-
	term health.
	Proceedings of the Nutrition Society 61 (01), pp. 71–77
	No GLP, published
7.	Li, S., Arning, E., Liu, C., Vitvitsky, V., Hernandez, C., Banerjee, R. et al. (2009). Regulation of homocysteine
	homeostasis through the transcriptional coactivator PGC-1 $\alpha$ .
	American Journal of Physiology - Endocrinology and Metabolism 296 (3), E543–8
	No GLP, published
8.	Baird, C.D., Nelson, M.M., Monie, I.W., Evans, H.M. Congenital cardiovascular anomalies induced by
	nteroylelutamic acid deficiency during sestation in the rat
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## 2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development

According to Regulation 1272/2008 (CLP), substances are classified for reproductive toxicity in Category 1A (known human reproductive toxicant) based largely on evidence from humans or in 1B (presumed human reproductive toxicant) or 2 (suspected human reproductive toxicant) largely based on animal data. The animal data required for 1B classification "shall provide clear evidence of an adverse effect on sexual function 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". Substances are classified in Category 2 when there is "some evidence from humans or experimental animals... of an adverse effect on sexual function or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1"

As there is no human data available for quinoclamine, the criteria for category 1A are not fulfilled.

The mainly manifestations of developmental toxicity noted in the studies that are considered potentially relevant for classification are: structural abnormalities (aortic arch abnormalities, skeletal abnormalities, hydronephrosis), altered growth and post-implantation loss noted in rats and rabbits. In the rat study by Anonymous 26 (2002), one case of severe oedema and one case of retro-oesophagal aortic arch were noted. These malformations were considered suitable for the setting of adversity but not enough for classification as the the incidences were low and observed in one species only at a high dose level.

## Aortic arch malformations:

In the rat study by Anonymous 25, 1986 (Report No.: AKJ/4/86) interrupted aortic arch (one foetus) was noted at the highest dose level of 75 mg/kg bw/day. In addition, the aortic malformations situs inversus (two foetuses) and innominate artery absent (four foetuses) were noted at this dose level. The incidence of situs inversus (mean% foetus: 0.8%) was outside the historical control data for the study-performing laboratory in 1985 (mean % foetus: 0.4%), while the defects innominate artery absent and interrupted aoartic arch were not presented in this historical control data. The defect innominate artery absent was also found at 20 mg/kg bw/day (one foetus). Maternal toxicity noted at 20 mg/kg bw/day was less marked and consisted of enlarged spleen noted in one dam only. At 75 mg/kg bw/day, maternal toxicity consisted of reduced bw gain (25%) and enlarged spleen noted in four dams.

In the rabbit study by Anonymous 27, 1986 (report No.: AKJ/3/86) aortic arch malformations were noted in two foetuses at the highest dose level of 22.5 mg/kg bw/day. The incidence (1.7%) was within historical control data for the study-performing laboratory in 1985 (2.2%). No adverse maternal toxicity was observed in this study (at

22.5 mg/kg bw/day: reduced bodyweight gain: 5%).

Incidences of aortic arch malformations (interrupted aortic arch) were also noted in the range finding study to the rabbit study by Anonymous 28, 1986 (Report No.: AKJ/1/86) at the dose level of 20 mg/kg bw/day (one foetuses) and 50 mg/kg bw/day (one foetuses).

<u>As a conclusion</u>, aortic arch malformations were noted in several studies and in both species, and could not be explained by maternal toxicity. The defect was considered severe and relevant for a classification for reproductive toxicity, although the incidences of aortic arch malformations were low and the effect was not reproducible in the studies by Anonymous 26/29 (2002).

## Skeletal abnormalities/variations:

In the rabbit study by Anonymous 29, 2002 (Report No.: 619/155-D6154) increased incidence of abnormal terminal caudal vertebrae was noted at 17.5 mg/kg bw/day (mean % foetuses: 5.6% compared to 2.3% in control) and 30 mg/kg bw/day (mean % foetuses: 6.4% compared to 2.3% in control). This effect was not present as variant in the historical control data in six preceding studies. The defect misaligned, connected or absent caudal vertebra was however present as malformation in these historical control data showing low incidences (mean % foetuses:

0-1%). Maternal toxicity was present at the dose levels of  $\geq$ 17.5 mg/kg bw/day. At 17.5 mg/kg bw/day reduced maternal bodyweight change (67% of control at Days 12-15) was noted. At 30 mg/kg bw/day maternal bodyweight change was reduced (46% of control) as well as maternal body weight (7%), and one dam was killed on Day 18 following severe inappetence. Furthermore, findings of misshapen nasal bone (5 foetuses, incidence mean% foetuses: 8% compared to 0% in control), absent frontal (5 foetuses, incidence mean % foetuses: 8.9% compared to 0% in control) and misaligned thoracic vertebral arch (one foetus) were noted in this rabbit study at the highest dose level (30 mg/kg bw/day). These defects were not present in the historical control data in six studies preceding the present study. Increased incidence of skeletal foetal variations such as incomplete ossification of frontal and maxilla bones, slight fusion of sternebrae, and asymmetric ossification of cervical vertebral centra were also noted in the study at 30 mg/kg bw/day. The skeletal abnormalities mentioned above were not observed in the rabbit study by Anonymous 27 (1986) and Anonymous 29 (2002) were not fully comparable, with the major differences being the length of dosing (Anonymous 27 study: DG 6-18; Anonymous 29 study: 7-28) and slightly higher doses in the study by Anonymous 29 (up to 30 mg/kg bw/day) compared to the dose levels used in the rabbit study by Anonymous 27 (up to 22.5 mg/kg bw/day).

In the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86) skeletal malformations were noted at the highest dose level (22.5 mg/kg bw/day). These malformations consisted of hyperextension of limb or paw noted in one animal, spina bifida noted in three animals, scoliosis noted in one animal and sternebral fusion noted in three animals. All incidences were within historical control data, except the incidence of fused sternebra (2.6%) which were outside background data of the laboratory in 1985 (0.7%). Increased incidence of skeletal variants were also

noted in this study at the highest dose level (22.5 mg/kg bw/day), and consisted of increased no. of caudal centra  $\leq$ 15 (84.9% compared to 59.9% in control). No adverse maternal toxicity was noted in this study (At 22.5 mg/kg bw/day: maternal bodyweight gain reduced 5%). The mentioned skeletal abnormalities/variants were not observed in the rabbit study by Anonymous 29 (2002).

In the rat study by Anonymous 26, 2002 (Report No.: 619/94-D6154) increased incidences of skeletal variations were noted at 20 mg/kg bw/day (incomplete ossification of skull bone and unossified fifth sternebrae) and 75 mg/kg bw/day (incomplete ossification of skull bone and unossified fifth sternebrae). These findings were considered to be secondary to maternal toxicity observed at these dose levels. At these dose levels maternal bodyweight gain was reduced (At 20 mg/kg bw/day: Days 7-8: 62%, Day 17-19: 21%; At 75 mg/kg bw/day: Days 17-19: 41%) and bodyweight loss was noted at 75 mg/kg bw/day (Days 6-7: -4.6 g, Days 7-8: -2.6g, Days 8-9: -0.4g).

Increased incidence of skeletal variations were also noted in the rat study by Anonymous 25, 1986 (Report No.: AKJ/4/86. At 20 and 75 mg/kg bw/day the incidence of following skeletal variations was increased: skull: hyoid non ossified, vertebrae: thoracic centre one or more bilobed. At 75 mg/kg bw/day increased incidence of sternebral variations were noted in addition (non ossified 5th and 6th sternebrae, one or more bilobed, bipartite or misaligned). Maternal toxicity noted at 20 mg/kg bw/day consisted of enlarged spleen in one dam. At 75 mg/kg bw/day, enlarged spleen was noted in 4 dams and maternal bodyweight gain was reduced 25% (Day 7-17). The findings of skeletal variations noted in this study were considered to be secondary to the maternal toxicity, although it could be noted that the maternal toxicity was not marked at the dose level of 20 mg/kg bw/day.

<u>As a conclusion</u>, findings of skeletal variations were noted in both sexes. These were considered to be secondary to the maternal toxicity. Increased incidences of abnormal terminal caudal vertebrae, misshapen nasal bone, absent frontal, misaligned thoracic vertebral arch were noted in the rabbit at high dose level and were outside the range of historical control data at time of study, or not present in this data. The defects were considered severe, and relevant for a classification for reproductive toxicity, although the incidences were low and the defects were observed in one species only.

## Hydronephrosis:

In the rabbit study by Anonymous 29, 2002 (Report No.: 619/155-D6154) findings of the malformation hydronephrosis were noted at dose levels of 17.5 (one animal) and 30 mg/kg bw/day (two animals). In addition, dose-related increased incidence of kidney cavitation was noted, statistically significant at 30 mg/kg bw/day. The incidence of hydronephrosis noted in this study was dose related. No findings of hydronephrosis were presented in the historical control data in six studies preceding the present study. Maternal toxicity noted at 17.5 mg/kg bw/day consisted of reduced body weight change (67% of control). At 30 mg/kg bw/day, maternal bodyweight change was reduced (46% of control) and one dam was killed following severe inappetence. There were no foetuses with hydronephrosis in the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86) using doses up to 22.5 mg/kg

bw/day. In the range finding study of Anonymous 28, 1986 (Report No.: AKJ/1/86), one single case of kidney left agenesis was found at the dose level of 50 mg/kg bw/day.

In the rat study by Anonymous 26, 2002 (Report No.: 619/94-D6154) findings of hydronephrosis were noted at the highest dose level of 75 mg/kg bw/day (3 animals). The incidence of hydronephrosis (1.1%) was slightly outside the control range (1.0%) of the six studies preceding the present study. Furthermore, a single case of misshapen kidney occurred at 75 mg/kg bw/day. No findings of misshapen kidney were presented in the historical control data. Maternal toxicity was present at the dose level of 20 mg/kg bw/day and above. Maternal bodyweight gain was reduced (At 20 mg/kg bw/day: Days 7-8: 62%, Day 17-19: 21%; At 75 mg/kg bw/day: Days 17-19: 41%) and bodyweight loss was noted at 75 mg/kg bw/day (Days 6-7: -4.6 g, Days 7-8: -2.6g, Days 8-9: -0.4g). There were no findings of hydronephrosis or misshapen kidney in the rat study by Anonymous 27, 1986 (Report No.: AKJ/3/86). However, it could be noted that the maternal effects were more marked in the study by Anonymous 26 (2002), which might be explained by a problem with the allocation of the animals indicating that younger animals were allocated in the mid- and high dose groups compared to the control group.

<u>As a conclusion</u>, findings of hydronephrosis were noted in both species. The incidences were outside the historical control range or not found in historical control data at time of study. Furthermore, one single case of misshapen kidney was noted in the rat study by Anonymous 26 (2002) at the highest dose level (75 mg/kg bw/day), and statistically significant increased incidence of kidney cavition was noted in the rabbit study by Anonymous 29 (2002) at the highest dose level (30 mg/kg bw/day). The defect hydronephrosis was considered severe and relevant for a classification for reproductive toxicity, although the incidences were low. The finding of kidney cavition noted in the rabbit was also considered relevant for classification, taking into account that the kidney is a target organ for quinoclamine.

## Foetal growth retardation:

In the rat study by Anonymous 25, 1986 (Report No.: AKJ/4/86) reduced foetal weight (7%) were noted at the dose level of 75 mg/kg bw/day. This effect was considered to be secondary to the maternal toxicity observed at this dose level. Maternal toxicity at this dose level consisted of reduced bodyweight gain (day 7-17: 25%) and enlarged spleen (4/24 animals).

In the rat study by Anonymous 34, 2002 (Report No.: 619/123-D6154) reduced foetal weight was noted at the dose level of 20 mg/kg bw/day (7%) and 75 mg/kg bw/day (12%). This effect was considered to be secondary to the maternal toxicity observed at these dose levels. At 20 mg/kg bw/day maternal reduced bodyweight gain (Days 7-8: 62%, Days 17-19: 21%) and reduced food consumption were noted. At 75 mg/kg bw/day maternal reduced bodyweight gain (Days 17-19: 41%), body weight loss (Days 6-7: -4.6 g, Days 7-8: -2.6 g, Days 8-9: -0.4 g) and reduced food consumption were noted.

In the rabbit study by Anonymous 27, 1986 (Report No.: AKJ/3/86) reduced foetal weight (5%, n.s.) was noted at the highest dose level of 22.5 mg/kg bw/day. This effect was considered to be secondary to the maternal toxicity

observed at this dose level. Minor maternal toxicity (reduced bodyweight gain, Days 0-28: 5%) was noted at 22.5 mg/kg bw/day.

<u>As a conclusion</u>, reduced foetal weight was noted in the rat (statistically significant, reductions up to 12%) and rabbit (not statistically significant). The effect was suitable for the setting of adversity, but not enough for classification for reproductive toxicity, as significant effects were noted in one species only and seen in association with marked maternal toxicity.

### Post-implantation loss:

In the rabbit study by Anonymous 29, 2002 (Report No.: 619/155-D6154), dose-related increased post-implantion loss were noted, but this effect was statistically significant only at the highest dose level (30 mg/kg bw/day). Maternal toxicity such as mortality (one dam) and reduced bodyweight (7%) were noted at 30 mg/kg bw/day, and reduced bodyweight changes were noted at 17.5 mg/kg bw/day (67% of control) and 30 mg/kg bw/day (46% of control).

In the rat study by Anonymous 26, 2002 (Report No.: 619/94-D6154) there were increases in both pre- and post-implantation losses noted at the highest dose level of 75 mg/kg bw/day. The incidence of post-implantation loss (11% compared to 5% in control) was not statistically significant but was higher than expected from the current background data (background data 4.0%-6.5%). The incidence of pre-implantation loss (17.4% compared to 8.6% in control) was not statistically significant and within live expected from the current background data (3.9%-24.3%). Maternal toxicity was adverse at  $\geq 20$  mg/kg bw/day. Maternal reduced bodyweight gain was noted at 20 mg/kg bw/day (Days 7-8: 62%, Days 7: 21%) and at 75 mg/kg bw/day (Days 17-19: 41%), and body weight loss was noted at 75 mg/kg bw/day (Days 6-7: -4.6 g, Days 7-8: -2.6 g, Days 8-9: -0.4 g).

<u>As a conclusion</u>, the effect on post-implantation loss observed in the rat- and rabbit developmental studies by Anonymous 26/29 (2002) was considered suitable for the setting of adversity but not enough for classification, as the incidence was observed mainly at maternal toxicity dose levels.

## Overall conclusion regarding adverse effects on developmental and RMS proposal for classification (RMS):

The findings of aortic arch malformations (noted in several studies and in both species), skeletal malformations i.e. abnormal terminal caudal vertebrae, misshapen nasal bone, absent frontal, misaligned thoracic vertebral arch (noted in the rabbit) and kidney effects i.e. hydronephrosis (noted in both species), misshapen kidney (one single case noted in rabbit) and increased incidence of kidney caviation (noted in rabbit) are considered relevant for a classification for reproductive toxicity. A classification for reproductive toxicity in Category 2 (Hazard Statement: H361d: Suspected of damaging fertility or the unborn child) is proposed for quinoclamine.

## 2.6.6.3 Adverse effects on or via lactation [equivalent to section 10.10.7 of the CLH report template]

Fable 2.6.6.3-1. Summary table of animal studies on effects on or via lactation							
Method, guideline,	Test substance, dose levels duration	Results	Reference				
deviations if any,	of exposure	- NOAEL/LOAEL (for sexual function					
species, strain, sex,	-	and fertility, parents)					
no/group		- target tissue/organ					
		- critical effects at the LOAEL (bold					
		text)					
Two generation	K-1616 (Quinoclamine)	<u>1 ppm:</u>	RAR Vol. 3,				
reproduction study		Parental:	B.6.6.1/01				
	Purity: 98.5%	-clinical signs (hunched posture F0/F1)					
In-house method		↓ bw (P1 M: 3%; P2 M: 7%; P2 F 4%)	Anonymous				
D. I	0, 1, 25, 500 ppm Corresponding to:	huy agin (D1 M, 40/ D2 M, 110/	19 (1975)				
Rat	F0: 0, 0.07, 1.6, 30.9  mg/kg bw/day in	$\downarrow$ Dw gall (P1 M: 4%, P2 M: 11%;	D (N				
Same and Davidan	males; 0, 0.08, 1.9 and 37.7 mg/kg	P2 F: 4%)	Report No.:				
Sprague-Dawley	$E_1 = 0.007 \pm 1.7$ and $27.0 \text{ mg/kg}$		834-111				
ме	$h_{1}^{11}$ (0,0.07, 1.7 and 37.0 mg/kg	Offenring	New data for				
141, 1	mg/kg bw/day in females	increased incidence of gray lung cysts in	the Annex I				
25/sex/group	ing/kg ow/day in temates	F2h offspring reared for 3 months (18	renewal: No				
20,800 group	The parents of both generations were	compared to 11 in control group)	Tene war. 100				
	fed the appropriate diets for at least	compared to 11 m condict group)					
	nine weeks and then subjected to two	25 ppm:					
Study was checked for	subsequent mating trials. Fresh diets	Parental:					
compliance with OECD	were prepared and presented weekly	-clinical signs (hunched posture F0/F1)					
TG 416 (2001) and	to the rats of all generations from	↓ bw (P1 M: 1%: P2 M: 7%: P2 F 5%)					
following deviations	initiation (P1) or weaning (F1b—>F2,						
were noted:	F2b)	$\downarrow$ bw gain (P1 M: 2%, P2 M: 11%;					
1. No evaluation of the		P2 F: 6%)					
oestrus cycles was		Offerencia es					
performed for enner		increased incidence of grav lung cysts in					
ii No examination of		F2h offspring reared for 3 months (29					
sperm parameters was		compared to 11 in control group)					
performed for either							
generation		<u>500 ppm:</u>					
iii. Gestation length was		Parental:					
not specified		-clinical signs (F0/F1: hunched posture)					
iv. organs were not		↓ <b>bw</b> (P1 M: 4%; P2 M: <b>10%</b> ;					
weighed		P2 F 10%)					
v. Vagina, testis,		<b>bw gain</b> (P1 M: 7% P2 M: 11%)					
vasiclas prostate and		$P_{2} = 0.0(2)$					
coagulating gland were							
not investigated		$\downarrow$ inter size in F2a and F2b generations					
microscopically		(mean litter size born in F2a generation:					
vi. Detailed testicular		4 males and 5 temales compared to 6					
histopathology was not		males and o remales in the control group; mean litter size horn in F2b generation: 5					
performed		males and 5 females compared to 7 males					
vu. Postlactational ovary		and 6 females in control group)					
(primoraial and growing							
youicies) histopathology was not performed		Offspring:					
viji For the offspring		-clinical signs (orange stained fur F2b					
age at vaginal opening		offspring)					
or PPS for the F1 and		$\downarrow$ <b>bw</b> during lactation (F1a: 13% and 7%					
F2 was not determined		in males and females, respectively;					

Table 2.6.6.3-1. Summary	y table of anima	l studies on effects	on or via lactation
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Method, guideline,	Test substance, dose levels duration	Results	Reference
deviations if any,	of exposure	- NOAEL/LOAEL (for sexual function	
species, strain, sex,	•	and fertility, parents)	
no/group		- target tissue/organ	
		- critical effects at the LOAEL (bold	
		text)	
GLP: No		F1b: 14% and 9% in males and females,	
		respectively; F2a: 8% and 9% in males	
		and females, respectively; F2b: 11% and	
		5% in males and lemales, respectively)	
		$\downarrow$ <b>litter size</b> in F2a and F2b generations	
		(mean litter size born in F2a generation: 4	
		males and 5 females compared to 6 males	
		and 6 females in the control group; mean	
		litter size born in F2b generation: 5 males	
		and 5 females compared to / males and 6	
		increased incidence of group	
		in F2h offspring reared for 3 months (30	
		compared to 11 in control group)	
		compared to 11 in control group)	
		NOAEL parental and offsprings: 25 ppm	
		(1.6 mg/kg bw/day)	
		NOAEL reproductive toxicity: 500 ppm	
		(37 mg/kg bw/day)	

#### Table 2.6.6.3-2. Summary table of human data on effects on or via lactation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data				

#### Table 2.6.6.3-3. Summary table of other studies relevant for effects on or via lactation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data				

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

Two generation reproductive toxicity study (RAR Vol. 3, B.6.6.2/01)

The study is no GLP study and considered limited due to several deviations from the OECD TG 416. In the study groups of 25 male and 25 female Sprague-Dawley rats received K-1616 (quinoclamine) in the diet at dose level up to 500 ppm (corresponding to 30.9 and 37.7 mg/kg bw/day in F0 males and females, respectively, and 37.0 and 43.8 mg/kg bw/day in F1 males and females, respectively) through two successive generations. Treatment with the test substance did not affect mating performance or fertility of the male and female parental animals and no consistent differences from control values were noted in comparisons of parental food consumption, survival rates and parturition indices or postnatal and postweaning survival. In addition, evaluations of the data obtained from foetuses taken by caesarean section did not reveal any findings indication teratogenic effects of the test substance at any of these concentrations. Differences from control group data noted at the high dose level (500 ppm) included lower growth period mean body weight values in the P1 (4% at week 13) and P2 (10% at week 9) generation males and P2 generation females (10% at week 9), reduced bodyweight gain in P1 (7%) and P2 (11%) generation males and P2 (9%) generation females, lower mean offspring weights at weaning in all filial generations (F1a: 13% and 7% in males and females, respectively; F1b: 14% and 9% in males and females, respectively; F2a: 8% and 9% in males and females, respectively; F2b: 11% and 5% in males and females, respectively), an increase in the observations of hunched appearance during the growth periods of both parental generations, and an increased incidence of gray lung cysts and orange-stained fur noted in the F2b offspring at necropsy. Mean litter size in F2a and F2b generations were also reduced at this dose level.

Differences noted to a lesser degree at the mid dose level (25 ppm) included slightly lower mean body weight values in the P1 (1% at week 13) and P2 (7% at week 9) generation males and P2 (5% at week 9) generation females at the last weighing interval of the growth periods, reduced bodyweight gain in P1 (2%) and P2 (11%) generation males and P2 (6%) generation females, an occasional slight increase in the observations of hunched appearance in both parental generations, and an increased incidence of gray lung cysts in the F2b offspring at necropsy.

Differences noted to a lesser degree at the low dose level (1 ppm) included slightly lower mean body weight values in the P1 (3%) and P2 (7%) generation males and P2 (4%) generation females at the last weighing interval of the growth periods, reduced bodyweight gain in P1 (4%) and P2 (11%) generation males and P2 (4%) generation females, an occasional slight increase in the observations of hunched appearance in both parental generations, and an increased incidence of lung cysts in the F2b offspring at necropsy.

Increased incidence of gray lung cysts was noted in the F2b offspring reared for three months (at 1 ppm: 18 compared to 11 in control group; at 25 ppm: 29 compared to 11 in control group; at 500 ppm: 39 compared to control group). The findings of gray lung cysts in the F2b offspring was dose related although the relevance of this finding is not clear. The finding was not observed in the offspring of the F1b generation reared for 5 weeks or in other available toxicological studies on quinoclamine. Thus, it seems to be a finding occurring in adult F2b animals including control animals. In the high dose group the incidence of gray cysts was 3.5 times higher when compared to controls, and considered adverse. In the low and mid-dose groups the incidences were less marked (1.6 to 2.6 times higher when compared to controls) and not considered adverse in the absence of other effects in the offspring at these dose levels.

The NOAEL for parental animals was set at 25 ppm (1.6 mg/kg bw/day) based on clinical signs (hunched posture) noted in P1 and P2 generation animals at 500 ppm (37 mg/kg bw/day), reduced body weight noted in P2 males and females at 500 ppm, and reduced bodyweight gain noted in P2 males at 500 ppm.
The NOAEL for offsprings was set at 25 ppm (1.6 mg/kg bw/day) based on reduced body weights at weaning in all filial generations noted at 500 ppm (37 mg/kg bw/day) and gray lung cysts in in P2 offspring reared for 3 months.

The NOAEL for reproductive toxicity was set at 500 ppm (37 mg/kg bw/day).

# 2.6.6.3.2 Comparison with the CLP criteria regarding effects on or via lactation

According to the CLP Guidance Table 3.7.1(b) a substance should be classified for lactation effects when the following applies:

"(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 likehood that the substance is present in potentially toxic levels in breast milk."

No data is available to address criterias (a) and (c). A reduction in pup weight was seen at a dose level (500 ppm) associated with maternal toxicity. Thus, the effect on pup bodyweight is not considered to "provide clear evidence of adverse effect in the offspring due to transfer in the milk".

# 2.6.6.4 Conclusion on classification and labelling for reproductive toxicity

Classification of quinoclamine as toxic for reproduction in Category 2, H361d ("Suspected of damaging fertility or the unborn child") is proposed.

# 2.6.7 Summary of neurotoxicity

# Table 2.6.7-1. Summary table of animal studies on neurotoxicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL	Reference
No data			

# 2.6.8 Summary of other toxicological studies

# 2.6.8.1 Toxicity studies of metabolites and impurities

## 2.6.8.1.1 Impurities

See Annex C

# 2.6.8.1.2 Metabolites

Quinoclamine is not intended for feed or food products. Accordingly, plant metabolites are not relevant for the evaluation.

Some studies on phtalic acid, a major photolusis metabolite in soil and under aquatic conditions – were found in the open literature and were submitted by the applicant (Vol. 3, B.6.8.1). One study investigated the toxicokinetics of phthalic acid and another study investigated the genotoxic potential. Two more studies investigated the endocrine disruptive properties of this metabolite.

As quinoclamine is not intended for feed or food products, and as an assessment of the relevance of metabolites for groundwater was not considered necessary (Vol. 1 section 2.11.6), the studies on phthalic acid were not given further significance for the evaluation of the active substance in this report, with exception of the two studies investigating the endocrine disruptive properties of phthalic acid (summarised in table below). These two studies were considered as supporting data with regard to the endocrine disruption evaluation (section 2.6.8.3)

Study/method	Substance	Results	Reference	Comments
In a molecular docking	Phthalic	For human androgen	Sarath, J. M. K.,	No GLP
study- using the docking	acid	receptor binding, the higher	Pradeep, S.,	study
software Glide		G scores (the highest was -	Vijayalekshmy, A.K.	
(Schrödinger)- the		8.19 kcal/mo1-1 for	S., Sudha Devi, R.,	The result of
molecular interactions of		testosterone) were seen with	Balachandran, S.,	this study
31 ligands, including 12		the natural ligands	Sreejith, M. N.,	indicates that
diphthalates, their		(controls). Phthalic acid	Sailas, B. (2016).	phtalic acid
monophthalates and		showed a lower G score (-	Human ketosteroid	may cause
phthalic acid with		5.49 kcal/mo1-1) indicating	receptors interact	endocrine
selected human		the ability to bind to human	with hazardous	disruption
ketosteroid receptors, i.e.,		androgen receptors but with	phthalate plasticizers	properties in
androgen (hAR),		lower affinity than the	and their metabolites:	vitro/in vivo
progesterone (hPR) and		natural ligands.	an in silico study.	
glucocorticoid (hGR)		For human progesterone	Journal of Applied	Study
receptors were explored		receptor bindind the highest	Toxicology, 36 (6),	considered
and their binding		G score was seen with the	p. 836–843	as supportive
affinities were compared		natural ligand		data
with that of		tetrahydrogestrinone (-9.43	Study summary by	
corresponding natural		kcal/mo1-1). Phthalic acid	the applicant is	
steroids and a known		showed a lower G score (-	presented in Vol. 3,	
endocrine disrupting		6.46 kcal/mo1-1).	B.6.8.1/03	

xenobiotic, bisphenol A (BPA). The G score as an empirical scoring function that approximates the ligand binding free energy was established. The higher the negative value of the G score, the higher is the affinity of the ligand to bind to the receptor.		For human glucocorticoid receptor binding, again phthalic acid showed a lower G score (-6.86 kcal/mo1-1) than the natural ligand cortisol (-7.76 kcal/mo1-1). The molecular receptor interactions of those phthalates showing the highest G scores where graphically presented in the original source. For phthalic acid no molecular interactions were presented. <u>As a conclusion</u> , phthalic acid was able to interact with human androgen, progesterone, and glucocorticoid receptors in <i>in silico</i> docking experiments. The binding affinity was lower compared to the natural ligands to the		
Amnion-derived WISH cells were obtained from ATCC (the American Type Culture Collection, CCL-25) and maintained in the laboratory. Cells were grown at 37°C in an atmosphere of 5% CO <sub>2</sub> :95% air, in a mixture of Ham's F12 and Dulbecco's modified Eagle medium (F12/DMEM; 1:1 v/v) supplemented with 10% fetal bovine serum (FBS), 30 mg/ml gentamicin and 0.25 mg/ml amphotericin B. The cells were seeded into 24-well plates at 2 x $10^5$ cells per well in F12/DMEM + 10% FBS and grown to confluence (2–3 days). WISH cells were plated in 24-well plates (2 x $10^5$ cells per well) and, at a 70% confluence, cells were preincubated for 1 h in the presence of 10 µM Ro 20-1724 (a cAMP phosphodiesterase inhibitor, suggesting that	Phthalic acid	It was demonstrated that phthalic acid (i) displaces $[^{3}H]$ estradiol from its binding sites (IC <sub>50</sub> = 89 nM, Ki = 66 nM), (ii) enhances the intracellular cyclic AMP concentration, without influencing adenylyl cyclase activity, (iii) stimulates or inhibits prostaglandin output, probably depending on the intracellular nucleotide level. 17 $\beta$ - estradiol exerts similar effects in WISH cells, and it was suggested by the authors that the molecular mechanisms underlying phthalic acid and steroid- hormone responses in this cell line are the same.	Pavan, B., Biondi, C., Ferretti, M. E., Lunghi, L., Paganetto, G. (2001). Phthalic acid mimics 17beta-estradiol actions in WISH cells. Toxicology letters 118 (3), p. 157–164. Study summary by the applicant is presented in Vol. 3, B.6.8.1/04	No GLP study The result of this study indicates that phtalic acid may cause endocrine disruption effects. Study considered as supportive data

cAMP level enhancement		
could induce estrogen		
receptor expression).		
Cells were washed with		
PBS, then incubated in		
the presence of ten		
different concentrations		
of [ <sup>3</sup> H] estradiol ranging		
from 5 to 250 nM for		
saturation experiments.		
For the competitive		
binding assays, cells were		
incubated in the presence		
of 10 nM [ <sup>3</sup> H] estradiol		
alone to determine		
specific binding, or in		
combination with nine		
different concentrations		
of phthalic acid ranging		
from 1 nM to 1 mM.		
Nonspecific binding was		
determined by adding 10 <sup>-5</sup>		
M diethylstilbestrol. All		
incubations were carried		
out at 37°C for 30 min, in		
a final volume of 0.5 ml		
of serum-free medium		
containing 20 mM		
NaMoO <sub>4</sub> . The unbound		
ligand was removed by		
washing the cells twice		
with PBS supplemented		
with 20 mM NaMoO4 and		
1 mg/ml BSA, and once		
with normal PBS. Cells		
were disrupted with 1 N		
NaOH (0.25 ml) and		
collected from the cluster		
dishes. Bound		
radioactivity was		
measured by scintillation		
spectrometry.		

# 2.6.8.2 Supplementary studies on the active substance

Type of	Test	Relevant	Observations	Reference
study/data	substance	information about		
		the study (as		
		applicable)		
Dermal	Quinoclamine	The study was	Maternal effects:	RAR Vol. 3, B.6.8.2/01
embryo-		performed to		
foetal	Purity: 97.7%	investigate the effects	5 mg/kg bw/day:	Anonymous 30 (1996)
development		of the test article on	-clinical signs (coloured urine)	
study		the embryonic and		Report No.: 1312-1416-001

·	r	f	Г	Γ
Type of	Test	Relevant	Observations	Reference
study/data	substance	information about		
		the study (as		
		applicable)		
	5, 100, 600	fetal development of	-macroscopical changes (reddish	
Rat	mg/kg	the rat when	discolouration of treated skin)	New data for the Annex I
	bw/day	administered during		renewal: No
In house		the period of	<u>100 mg/kg bw/day:</u>	
method	Vehicle: 1%	organogenesis. Three	-clinical signs (encrusted skin,	
	Tween 80	groups of twenty five	coloured urine)	
GLP: Yes		sexually mature and	-macroscopical changes (reddish	
	Day 6 to 15	mated female Sprague	discolouration of treated skin)	
	post-coitum	Dawley Crl:CD		
		(SD)BR rats (8-12	<u>600 mg/kg bw/day:</u>	
		weeks old) received	-clinical signs (encrusted skin,	
		Quinoclamine by	coloured urine)	
		dermal application at	↓ <b>bw loss</b> (Days 6-9: -0.41 g)	
		dose levels of 5, 100	↓ <b>bw gain</b> (Days 6-16: 31%)	
		and 600 mg/kg	↓FC	
		bw/day for 10	-macroscopical changes (reddish	
		consecutive days from	discolouration of treated skin)	
		day 6 to 15 post-		
		coitum, inclusive.	No embryotoxicity or	
			teratogenicity was noted in this	
			study	
			The study is considered as	
			supplementary data	
	L	I	suppression y data	

Treatment was associated with clinical signs (coloured urine noted at  $\geq$ 5 mg/kg bw/day and encrusted skin noted at  $\geq$ 100 mg/kg bw/day), reduced bodyweight growth noted at 600 mg/kg bw/day (bodyweight loss: -0.41 g, reduced bodyweight gain Days 6-16: 31%), reduced food consumption, and macroscopical changes (reddish discolouration of treated skin). No embryotoxicity or teratogenicity was noted in this study. The study was considered as supplementary data. The test substance was administered dermally instead of orally. The choice of administration route was not justified in study report.

# 2.6.8.3 Endocrine disrupting properties

The applicant has provided an assessment of potential endocrine properties of quinoclamine in a kind of WoE approach including an assessment of the available toxicity studies, a literature search and an assessment to identify structural alerts for hormonal activity using the OECD QSAR Toolbox (Vol. 3, B.6.8.3/01). The applicant has also provided an assessment of possible hyperglycaemic effects of quinoclamine including an assessment of available toxicity studies (Vol. 3, B.6.8.3/02).

Effects on endocrine organs (organ weight changes and histopathological changes) were noted in the standard toxicity studies on quinoclamine (Table 2.6.8.3-01 to 03 below). Changes in organ weights were noted for the adrenal (rat, dog), thyroidea (rat, dog), and ovary/uterus (dog). Histopathological changes were noted in the adrenal (rat, mouse, dog), testis (dog) and uterus (rat), and female mammary gland (rat). Post-implantation loss and reduced foetal weights were noted in the reproductive toxicity studies in the rat and rabbit.

In the assessment of possible hyperglycaemic effects of quinoclamine there were no evidence for secondary effects of hyperglycaemia (Vol. 3, B.6.8.3/02).

The open literature search performed by the applicant was restricted to results obtained for the active substance. However, having a look into the literature search for the metabolites, one in vitro study in the zebrafish was present for the metabolite phthalmic acid (Vol. 3, B.9.2.3). Phthalic acid was also able to interact with human androgen, progesterone, and glucocorticoid receptors in one in silico study (Vol. 3, B.6.8.1). Furthermore, phthalic acid was shown to mimics 17beta-estradiol actions in WISH cells in one in vitro study (Vol. 3, B.6.8.1). The results of these studies indicate that the metabolite phthalic acid may affect endocrine function.

No structural alerts were identified for quinoclamine indicating estrogenic activity in the QSAR analysis using OECD QSAR Toolbox.

# Conclusion by RMS:

There were some effects on endocrine organs in the standard toxicity studies on quinoclamine, but no clear effect pattern was shown. The effects occurred mainly at high dose levels, and thus could be due to systemic toxicity. However, there were also some effects noted at lower dose levels that could not clearly be explained (90-day dog study: loss of estrous cyclic activity, increased thyroid weight). Although no clear pattern was shown these effects might indicate an endocrine activity of quinoclamine, also considered that increased incidence of post-implantation loss was noted in one rabbit study at a dose level without maternal toxicity. The effect of increased post-implantation loss could be considered as a parameter sensitive to but not diagnostic of EATS (estrogen, androgen, thyroid, steroidogenic). Furthermore, open literature data gives some indications of endocrine effects caused by the metabolite phthalic acid.

It could also be noted that the potential for endocrine effects have not been fully investigated in available toxicity studies due to limitations in the test guideline available at the time. For example, sperm parameters and oestrus cycles have not been investigated in the reproduction toxicity study. Nor have gestation length, vaginal opening or preputial separation been determined.

Furthermore, the assessment to identify structural alerts for hormonal activity using the OECD QSAR Toolbox was restricted to predict estrogen receptor binding affinity. No other pathways such as androgen receptor pathway was performed.

<u>As a conclusion</u> there are some effects that might indicate endocrine activity. It could also be noted that limited endocrine parameters have been investigated in available studies.

Quinoclamine is proposed to be classified as toxic for reproduction in Category 2 and as carcinogenic in Category 2, thus, meets the interim criteria for endocrine disruptions as specified in Plant Protection Product Regulation (EC) No. 1107/2009. Interim criteria will be applied until final criteria are implemented (EFSA. Technical report

on outcome of pesticides peer review meeting on recurring issues in mammalian toxicology. Approved: 25 July 2016).

The opinion of RMS is that the substance fulfils the interims criteria for endocrine disrupters based on available data. Further discussions will however be needed in the light of the new guidance document before a final decision is taken.

#### Table 2.6.8.3-01: Effects noted in reproductive endocrine organs

Study	NOAEL in study	Effect on endocrine organ	Other effects at the dose level of effect on endocrine organs	Comments by study author	Comments by RMS
Testes	1			1	1
Oral (dietary) 2-year	NOAEL for both sexes was set at 10 ppm (0.33 and 0.31 mg/kg	<u>At 1000 ppm (26.6</u> mg/kg bw/day):	At 1000 ppm (26.6 mg/kg bw/day):	The animals appeared unhealthy with several further	Effects on testes were noted at a dose level with marked
(RAR Vol 3,	bw/day in males and females,		-mortality (one of each sex	signs of general toxicity	toxicity and might be due to
B.6.3.3.1/01)	respectively) based on mortalities	Testes:	sacrificed in extremis during	(anaemia, hepatotoxicity) and	systemic toxicity.
	noted in both sexes at 1000 ppm,	-small and soft	week 65)	several histomorphological	
In house method	reduced bodyweight gain noted	-aspermatogenesis	-clinical signs (brown-tined urine,	alterations (lung, liver, kidney,	No abnormalities were
	in both sexes at $\geq$ 250 ppm,	-athrophy	orange stained hair around	adrenals). Thus, the general bad	detected in the 90-day
Dog	changes in haematological	-focal nonsuppurative	urogenital area, during the second	health conditions of the affected	toxicity dog study using
Beagle	parameters (indicating anaemia)	orchitis	year of study: pale appearing oral	animals might be the cause for	dose levels up to 30 mg/kg
	noted in both sexes at $\geq$ 50 ppm,		mucosal membranes, yellowish	the observed testicular lesions.	bw/day.
M, F	changes in biochemical		discoloration of the eyes and		
4/sex/dose	parameters (indicating		thinness in the female sacrificed	The reduction in testis weigth	
	hepatotoxicity) noted in both		in extremis, and unhealthy	in dogs would suit an estrogen	
GLP: Yes	sexes at $\geq$ 250 ppm, statistically		appearance characterized by	agonist effect but lack of	
	significant changes in relative		thinness and lethargy in the male	histopathological effect in the	
	organ weights (lung, spleen and		sacrificed in extremis)	prostate (increased prostatic	
Dose levels:	gonads) noted in females at 1000		$\downarrow$ <b>bw</b> (week 52: M: 21%, F: 26%;	size and wegith by hyperplasia	
0, 2, 10, 50, 250 and	ppm, changes in gross pathology		week 104: M: 23%, F: 33%)	of the fibromuscular stroma and	
1000 ppm (equivalent	noted at 50 ppm (urinary bladder,		$\downarrow$ bw gain or bw loss (Weeks	squamous metaplasia of the	
to $0, 0.06, 0.33, 1.42,$	spleen, ovary) and 250 ppm		0-52: M: 0.3% compared to 2.4%	glandular epithelium) would	
7.62 and 26.6 mg/kg	(urinary bladder, spleen, liver,		in controls, F:-0.6% compared to	argue rather against. The same	
$\frac{DW}{day}$ in males, and $\frac{DW}{day}$ in males, and	ovary, kidneys) and 1000 ppm		1.7% in controls; weeks 52-104:	applies to an androgen excess; a	
0, 0.00, 0.51, 1.59,	(urinary bladder, spieen, ovary,		M: 0.1% compared to 1.2% in	characterized disturbed	
0.79 and 29.1 mg/kg	tostos overu hoart lung		E: 0.6%  compared to  1.5%  in	spermatogenesis is usually	
Dw/day in tentales)	mesonteria lymph nodes) and		F0.0% compared to 1.5% in	accompanied by an unchanged	
	histopathological changes noted		changes in haematological	the affected dogs however we	
	in the liver (in females at $>50$		<b>-changes in nacinatological</b>	see a significant reduction in	
	nn the river (in remains at $\geq 50$ ppm: in males at $\geq 250$ ppm)		intervals: haemoglobin M: up to	prostate weight and no	
	urinary bladder (in both seves at		26% F· up to $47%$ [haematocrit	significant histological	
	>50 ppm), adrenals (in both		(M, F), erythrocytes $(M, F)$ :	abnormalities.	
	sexes at $\geq 250$ ppm), lungs (in		$\uparrow$ platelet counts (F: week 104)		
	both sexes at $\geq 250$ ppm), spleen		-changes in biochemistry:		
	(in males at 1000 ppm; in		(†serum glutamic-pyruvic		

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females at ≥250 ppm), kidneys	transaminase (M, F), ↑alkaline	
(in both sexes at 1000 ppm,	phosphatase (M, F), ↑bilirubin	
mesenteric lymph node (in	(F: weeks 52, 78), ↑serum	
females at 1000 ppm), gall	glutamineo-oxaloacetic	
bladder (in both sexes at 1000	transaminase (M, F))	
ppm), pancreas (in females at	-changes in organ weights:	
1000 ppm), aorta (one female at	↑rel lungs (92%) (F),	
1000 ppm), testis (1000 ppm)	$\uparrow$ rel spleen (77%) (F), $\uparrow$ rel	
and ovaries (1000 ppm)	gonads (80%) (F), trel gonads	
	(55%) M, n.s),	
	$\downarrow$ rel prostate (45%), n.s))	
	-macroscopical changes in the	
	liver (enlarged, lobes thickened	
	and pale, rough surface and	
	mottled, brown in colour, tough in	
	consistency, firm), gall bladder	
	(distended, walls thickened),	
	kidneys (small, depressed areas	
	on surface, contracted, polycystic-	
	primarily in the medulla, cortex	
	collapsed, thickened and opaque	
	areas on capsule), urinary bladder	
	(brown mucosa or tan in colour,	
	wall thickened, omentum adhered	
	to serosal surface), <u>spleen</u> (dark in	
	colour or margins dark, enlarged),	
	testes (small and soft), prostate	
	(small at week 52), ovary (cyst on	
	one), heart (reddish-brown	
	discoloration at coronary grove,	
	right A/V valve thickened and	
	vascular with dark raised area	
	near point of attachment at week	
	52), <u>lung</u> (raised yellow gray foci	
	on all lobes, focal emphysematous	
	appearing areas), <u>cartilage</u>	
	(yellow to brown in colour),	
	trachea (brown or gray	
	discoloration), <u>ribs</u> (brown of gray	
	discoloration), <u>tendons</u> (brown or	
	gray discoloration), <u>bones</u> (gray in	

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	colour), mesenteric lymph nodes	
	(dark in colour), small intestine	
	(walls slightly thickened)	
	-histopathological changes in	
	adrenal (†vacuolation of cortical	
	cells (M,F), necrosis, one female),	
	lung (foci of foamy macrophages	
	(M,F), focal pneumonitis (M, F),	
	cholesterol clefts (M,F), fibrosis	
	(one female), edema (M,F),	
	consolidation (one male)), spleen	
	(extramedullary haematopoesis	
	and congestion (M,F)), liver	
	(pigment in cytoplasm of	
	hepatocytes, kuppfer cells and	
	macrophages (M,F), periportal	
	fibrosis (M,F), bile duct	
	proliferation (M,F), bile plugs in	
	canaliculi (M,F), sinusoidal	
	distension (F)), kidney (tubular	
	nephropathy with fibrosis and	
	renal tubular regeneration (M,F)),	
	urinary bladder (pigment in	
	mucosal cells (M,F), edema (one	
	female), pigment laden	
	macrophages (one female)), testis	
	(aspermatogenesis, testicular	
	atrophy, focal nonsuppurative	
	orchitis), ovary (lack of follicle	
	development, follicular cysts (one	
	female), mesenteric lymph nodes	
	(edema, erythrophagocytosis,	
	distension of medullary sinuses	
	(F)), <u>pancreas</u> (edema (F)), <u>gall</u>	
	bladder (hyperplasia (M,F),	
	papillary infolding (M,F),	
	cholelith (one female)), aorta	
	(mineralisation in one female),	
	small intestine (focal enteritis	
	(one female), erosion (one	
	female))	

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Prostate					
Oral (dietary) 2-year	NOAEL for both sexes was set at	<u>At 1000 ppm (26.6</u>	At 1000 ppm (26.6 mg/kg	Since these animals lost body	The effect on prostate was
(RAR Vol 3,	10 ppm (0.33 and 0.31 mg/kg	<u>mg/kg bw/day):</u>	<u>bw/day):</u>	weight and showed a reduced	noted at a dose level with
B.6.3.3.1/01)	bw/day in males and females,		-mortality (one of each sex	body weight gain, this loss in	marked toxicity and might
	respectively) based on mortalities	Prostate:	sacrificed in extremis during	prostate weight was assumed to	be due to systemic toxicity.
In house method	noted in both sexes at 1000 ppm,	small at week 52	week 65)	be rather due to the poor	No histopathological
	reduced bodyweight gain noted		-clinical signs (brown-tined urine,	general conditions than	changes were noted in the
Dog	in both sexes at $\geq 250$ ppm,		orange stained hair around	provoked by endocrine	prostate.
Beagle	changes in haematological		urogenital area, during the second	influence. There were no	
	parameters (indicating anaemia)		year of study: pale appearing oral	accompanying	
M, F	noted in both sexes at $\geq$ 50 ppm,		mucosal membranes, yellowish	histopathological abnormalities,	
4/sex/dose	changes in biochemical		discoloration of the eyes and	neither in the prostate nor in the	
	parameters (indicating		thinness in the female sacrificed	seminal vesicles.	
GLP: Yes	hepatotoxicity) noted in both		in extremis, and unhealthy		
	sexes at $\geq 250$ ppm, statistically		appearance characterized by		
	significant changes in relative		thinness and lethargy in the male		
Dose levels:	organ weights (lung, spleen and		sacrificed in extremis)		
0, 2, 10, 50, 250 and	gonads) noted in females at 1000		↓ <b>bw</b> (week 52: M: 21%, F: 26%;		
1000 ppm (equivalent	ppm, changes in gross pathology		week 104: M: 23%, F: 33%)		
to 0, 0.06, 0.33, 1.42,	noted at 50 ppm (urinary bladder,		$\downarrow$ <b>bw gain or bw loss</b> (Weeks 0-		
7.62 and 26.6 mg/kg	spleen, ovary) and 250 ppm		52: M: 0.3% compared to 2.4% in		
bw/day in males, and	(urinary bladder, spleen, liver,		controls, F:		
0, 0.06, 0.31, 1.39,	ovary, kidneys) and 1000 ppm		-0.6% compared to 1.7% in		
6.79 and 29.1 mg/kg	(urinary bladder, spleen, ovary,		controls; Weeks 52-104: M: 0.1%		
bw/day in females)	liver, gall bladder, kidneys,		compared to 1.2% in controls,		
	testes, ovary, heart, lung,		F: -0.6% compared to 1.5% in		
	mesenteric lymph nodes) and		controls)		
	histopathological changes noted		-changes in haematological		
	in the liver (in females at $\geq 50$		parameters (all post treatment		
	ppm; in males at $\geq$ 250 ppm),		intervals: the moglobin M: up to		
	urinary bladder (in both sexes at		26%, F: up to $4/\%$ thaematocrit		
	$\geq$ 50 ppm), adrenals (in both		$(M, F)$ , $\downarrow$ erythrocytes $(M, F)$ :		
	sexes at $\geq$ 250 ppm), lungs (in		↑platelet counts (F: Week 104)		
	both sexes at $\geq$ 250 ppm), spleen		-changes in biochemistry:		
	(in males at 1000 ppm; in		(†serum glutamic-pyruvic		
	temales at $\geq$ 250 ppm), kidneys		transaminase (M, F), ↑alkaline		
	(in both sexes at 1000 ppm,		phosphatase (M, F), ↑bilirubin (F:		
	mesenteric lymph node (in		weeks 52, /8), <sup>†</sup> serum		
	females at 1000 ppm), gall		glutamineo-oxaloacetic		
	bladder (in both sexes at 1000		transaminase (M, F))		

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ppm), pancreas (in females at	-changes in organ weights: ↑rel	
1000 ppm), aorta (one female at	lungs (92%) (F), $\uparrow$ rel spleen	
1000 ppm), testis (1000 ppm)	(77%) (F), <i>frel gonads</i> (80%) (F),	
and ovaries (1000 ppm)	↓rel gonads (55%) M, n.s), ↓rel	
	prostate (45%), n.s))	
	-macroscopical changes in the	
	liver (enlarged, lobes thickened	
	and pale, rough surface and	
	mottled, brown in colour, tough in	
	consistency, firm), gall bladder	
	(distended, walls thickened),	
	kidneys (small, depressed areas	
	on surface, contracted, polycystic-	
	primarily in the medulla, cortex	
	collapsed, thickened and opaque	
	areas on capsule), <u>urinary bladder</u>	
	(brown mucosa or tan in colour,	
	wall thickened, omentum adhered	
	to serosal surface), <u>spleen</u> (dark in	
	colour or margins dark, enlarged),	
	testes (small and soft), prostate	
	(small at week 52), <u>ovary</u> (cyst on	
	one), <u>heart</u> (reddish-brown	
	discoloration at coronary grove,	
	right A/V valve thickened and	
	vascular with dark raised area	
	near point of attachment at week	
	52), <u>lung</u> (raised yellow gray foci	
	on all lobes, focal emphysematous	
	appearing areas), <u>cartilage</u>	
	(yellow to brown in colour),	
	trachea (brown or gray	
	discoloration), <u>ribs</u> (brown of gray	
	discoloration), tendons (brown or	
	gray discoloration), <u>bones</u> (gray in	
	colour), mesenteric lymph nodes	
	(dark in colour), small intestine	
	(walls slightly thickened)	
	-histopathological changes in	
	adrenal (†vacuolation of cortical	
	cells (M,F), necrosis, one female),	

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			<u>lung</u> (foci of foamy macrophages (M,F), focal pneumonitis (M, F), cholesterol clefts (M,F), fibrosis (one female), edema (M,F), consolidation (one male)), <u>spleen</u> (extramedullary haematopoesis and congestion (M,F)), <u>liver</u> (pigment in cytoplasm of hepatocytes, kuppfer cells and macrophages (M,F), periportal fibrosis (M,F), bile duct proliferation (M,F), bile plugs in canaliculi (M,F), sinusoidal distension (F)), <u>kidney</u> (tubular nephropathy with fibrosis and renal tubular regeneration (M,F)), <u>urinary bladder</u> (pigment in mucosal cells (M,F), edema (one female), pigment laden macrophages (one female)), <u>testis</u> (aspermatogenesis, testicular atrophy, focal nonsuppurative orchitis), <u>ovary</u> (lack of follicle development, follicular cysts (one female), <u>mesenteric lymph nodes</u> (edema, erythrophagocytosis, distension of medullary sinuses (F)), <u>pancreas</u> (edema (F)), <u>gall</u> <u>bladder</u> (hyperplasia (M,F), papillary infolding (M,F), cholelith (one female)), <u>aorta</u> (mineralisation in one female), <u>small intestine</u> (focal enteritis (one female), erosion (one female))		
Ovary					
Oral (dietary) 2-year	NOAEL for both sexes was set at	<u>50 ppm:</u>	<u>50 ppm:</u>	After 104 weeks all high dose	Loss of cyclic activity was
(RAR Vol 3, B.6.3.3.1/01)	10 ppm (0.33 and 0.31 mg/kg bw/day in males and females, respectively) based on mortalities	Ovary: one small in size 250 ppm:	↓bw (M: week 52: 3%, week 104: 8%; F: week 52: 2%, week 104: 5%)	animals showed absence of developing follicles and therefore a loss of cyclic	noted at a dose level with marked toxicity.

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In house method	noted in both sexes at 1000 ppm,	Ovary: cyst on one	↓bw gain (Week 0-52: M: 2.6%	activity. The body weight of	The effects on ovary noted
	reduced bodyweight gain noted		compared to 2.4% in controls,	high dose animals is markedly	at 50 ppm (one small in
Dog	in both sexes at $\geq$ 250 ppm,	<u>1000 ppm:</u>	F: 2.3% compared to 1.7% in	lower than in the other dosing	size) and 250 ppm (cyst on
Beagle	changes in haematological	Ovary: lack of follicle	controls; Week 52-104: M: 0.1%	groups. The bitches of the high	one) could not be explained
	parameters (indicating anaemia)	development and	compared to 1.2% in controls,	dose group even lost body	by marked toxicity.
M, F	noted in both sexes at $\geq$ 50 ppm,	follicular cysts in one	F: 0.9% compared to 1.5% in	weight during the study in	However, the incidence
4/sex/dose	changes in biochemical	5	controls)	contrast to the other females	was low.
	parameters (indicating		-changes in haematological	involved who gained weight as	
GLP: Yes	hepatotoxicity) noted in both		parameters haematocrit (M.	expected. The animals appeared	
	sexes at $>250$ ppm, statistically		Week 76).  ervthrocytes	unhealthy with several further	
	significant changes in relative		(M Week 76, F Week 104)	signs of general toxicity	
Dose levels:	organ weights (lung, spleen and		-macroscopical changes in ovary	(anaemia, hepatotoxicity) and	
0, 2, 10, 50, 250 and	gonads) noted in females at 1000		(one small in size), urinary	several histomorphological	
1000 ppm (equivalent	ppm, changes in gross pathology		bladder (mucosa brown or tan in	alterations (lung, liver, kidney,	
to 0, 0.06, 0.33, 1.42.	noted at 50 ppm (urinary bladder.		colour), spleen (dark in colour or	adrenals). It is reasonable to	
7.62 and 26.6 mg/kg	spleen, ovary) and 250 ppm		margins dark))	assume that those bad	
bw/day in males, and	(urinary bladder, spleen, liver,		-histopathological changes in	conditions may lead to	
0. 0.06. 0.31. 1.39.	ovary, kidneys) and 1000 ppm		lung (focal pneumonitis (one	infertility and it is highly likely	
6.79 and $29.1$ mg/kg	(urinary bladder, spleen, ovary,		male)), liver (pigment in	that the lack of cyclicity is due	
bw/day in females)	liver, gall bladder, kidneys.		macrophages (one female), bile	to the reduction in body weight	
, <b></b> ,,	testes, ovary, heart, lung.		plugs in canaliculi (one female)).	and should not be considered as	
	mesenteric lymph nodes) and		urinary bladder (pigment in	triggered by endocrine	
	histopathological changes noted		mucosal cells (M, F))	mechanism	
	in the liver (in females at $>50$				
	ppm: in males at $\geq 250$ ppm).		250 ppm:		
	urinary bladder (in both sexes at		-clinical signs (brown-tined		
	$\geq$ 50 ppm) adrenals (in both		urine)		
	sexes at $\geq 250$ ppm) lungs (in		bw (week 104: M: 8% F: 6%)		
	both sexes at >250 ppm), range (in		$ \mathbf{b}\mathbf{w} $ gain or $\mathbf{b}\mathbf{w} $ loss (week 0-52)		
	(in males at 1000 ppm; in		M: 1.9% compared to 2.4% in		
	females at >250 ppm) kidneys		controls F. 2% compared to 1.7%		
	(in both sexes at 1000 ppm)		in controls, week 52-104:		
	mesenteric lymph node (in		$M^{\circ}$ -0.1% compared to 1.2% in		
	females at 1000 ppm) gall		controls F: 0.1% compared to		
	bladder (in both sexes at 1000		1.5% in controls)		
	ppm), pancreas (in females at		-changes in haematological		
	1000 ppm), aorta (one female at		parameters (haemoglobin (M:		
	1000 ppm), testis (1000 ppm)		week 26: 16%		
	and ovaries (1000 ppm)		week 52: 17%		
			week 76: 12%:		
			F: week 26: 16%.		

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	week 76: 20%), ↓haematocrit	
	(141. WEEKS 20, 32, $70$ , F. Weeks 26, 76, 104)	
	1. WEERS 20, 70, 104), Lervithrocytes (M: Weeks 26, 52	
	$104 \cdot \text{E} \cdot \text{Weeks} 76 \cdot 104 \cdot \text{e}$	
	-changes in biochemistry	
	(†serum glutamic-pyruvic	
	transaminase (M F) Alkaline	
	phosphatase (M F) †serum	
	glutamic-oxaloacetic	
	transaminase (M F))	
	-macroscopical changes in	
	urinary bladder (mucosal surface	
	brown or vellow-gray), liver	
	(brown in colour, rough surfaced.	
	tough in consistency, firm)	
	spleen (dark in colour or margins	
	dark), kidneys (depressed areas on	
	surface), ovary (cyst on one). lung	
	(white foci on surface)	
	-histopathological changes in	
	adrenal (\vacuolation of cortical	
	cells (M,F), focal nonsupparative	
	adrenalitis (one male)), lung (foci	
	of foamy macrophages $(M,F)$ ),	
	spleen (extramedullary	
	haematopoesis (F), congestion	
	(F)), liver (pigment in cytoplasm	
	of hepatocytes and kuppfer cells	
	(M,F), pigment in macrophages	
	(F), periportal fibrosis (M,F), bile	
	duct proliferation (M,F), bile	
	plugs in canaliculi (one female),	
	sinusoidal distension (F)), kidney	
	(tubular nephrosis (one female),	
	urinary bladder (pigment in	
	mucosal cells (M,F), pigment	
	laden macrophages (F))	

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	A 1000 (000 II	
	<u>At 1000 ppm (26.6 mg/kg</u>	
	<u>DW/day):</u>	
	-mortality (one of each sex	
	sacrificed in extremis during	
	week 65)	
	-crimical signs (brown-timed urine,	
	urogenital area, during the second	
	vear of study: pale appearing oral	
	mucosal membranes, vallowish	
	discoloration of the eyes and	
	thinness in the female sacrificed	
	in extremis and unhealthy	
	appearance characterized by	
	thinness and lethargy in the male	
	sacrificed in extremis)	
	<b>bw</b> (week 52: M: 21%. F: 26%:	
	week 104:	
	M: 23%, F: 33%)	
	<b>bw gain or bw loss</b> (Weeks 0-	
	52: M: 0.3% compared to 2.4% in	
	controls, F:-0.6% compared to	
	1.7% in controls;	
	Weeks 52-104: M: 0.1%	
	compared to 1.2% in controls,	
	F: -0.6% compared to 1.5% in	
	controls)	
	-changes in haematological	
	parameters (all post treatment	
	intervals: ↓haemoglobin M: up to	
	26%, F: up to 47% ↓haematocrit	
	$(M, F)$ , $\downarrow$ erythrocytes $(M, F)$ :	
	↑platelet counts (F: Week 104)	
	-changes in biochemistry:	
	(†serum glutamic-pyruvic	
	transaminase (M, F), ↑alkaline	
	phosphatase (M, F), ↑bilirubin	
	(F: Weeks 52, 78), ↑serum	
	glutamineo-oxaloacetic	
	transaminase (M, F))	

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	-changes in organ weights:	
	↑rel lungs (92%) (F),	
	↑ rel spleen (77%) (F), ↑rel	
	gonads (80%) (F), ↓rel gonads	
	(55%) M, n.s),	
	$\downarrow$ rel prostate (45%), n.s))	
	-macroscopical changes in the	
	liver (enlarged, lobes thickened	
	and pale, rough surface and	
	mottled, brown in colour, tough in	
	consistency, firm), gall bladder	
	(distended, walls thickened),	
	kidneys (small, depressed areas	
	on surface, contracted, polycystic-	
	primarily in the medulla, cortex	
	collapsed, thickened and opaque	
	areas on capsule), <u>urinary bladder</u>	
	(brown mucosa or tan in colour,	
	wall thickened, omentum adhered	
	to serosal surface), spleen (dark in	
	colour or margins dark, enlarged),	
	testes (small and soft), prostate	
	(small at week 52), ovary (cyst on	
	one), <u>heart</u> (reddish-brown	
	discoloration at coronary grove,	
	right A/V valve thickened and	
	vascular with dark raised area	
	near point of attachment at week	
	52), <u>lung</u> (raised yellow gray foci	
	on all lobes, focal emphysematous	
	appearing areas), <u>cartilage</u>	
	(yellow to brown in colour),	
	trachea (brown or gray	
	discoloration), <u>ribs</u> (brown of gray	
	discoloration), tendons (brown or	
	gray discoloration), bones (gray in	
	colour), mesenteric lymph nodes	
	(dark in colour), small intestine	
	(walls slightly thickened)	
	-histopathological changes in	
	adrenal (†vacuolation of cortical	

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			cells (M,F), necrosis, one female), <u>lung</u> (foci of foamy macrophages (M,F), focal pneumonitis (M, F), cholesterol clefts (M,F), fibrosis (one female), edema (M,F), consolidation (one male)), <u>spleen</u> (extramedullary haematopoesis and congestion (M,F)), <u>liver</u> (pigment in cytoplasm of hepatocytes, kuppfer cells and macrophages (M,F), periportal fibrosis (M,F), bile duct proliferation (M,F), bile plugs in canaliculi (M,F), sinusoidal distension (F)), <u>kidney</u> (tubular nephropathy with fibrosis and renal tubular regeneration (M,F)), <u>urinary bladder</u> (pigment in mucosal cells (M,F), edema (one female), pigment laden macrophages (one female)), <u>testis</u> (aspermatogenesis, testicular atrophy, focal nonsuppurative orchitis), <u>ovary</u> (lack of follicle development, follicular cysts (one female), <u>mesenteric lymph nodes</u> (adama arythyophagocytosis		
			distension (F)), <u>kidney</u> (tubular nephropathy with fibrosis and		
			nephropathy with fibrosis and renal tubular regeneration (M.F)).		
			urinary bladder (pigment in		
			mucosal cells (M,F), edema (one		
			remaie), pigment laden		
			(aspermatogenesis, testicular		
			atrophy, focal nonsuppurative		
			orchitis), ovary (lack of follicle		
			development, follicular cysts (one		
			female), <u>mesenteric lymph nodes</u>		
			distension of medullary sinuses		
			(F)), pancreas (edema (F)), gall		
			<u>bladder (hyperplasia (M,F),</u>		
			papillary infolding (M,F),		
			cholelith (one female)), <u>aorta</u>		
			(mineralisation in one female),		
			(one female), erosion (one		
			female))		
Uterus (and ovary)					
Oral (capsules) 90-	NOAEL for both sexes was set at	Uterus (and ovary)	<u>3 mg/kg bw/day:</u>	The study report states that	It is stated by study author
day study	3 mg/kg bw/day based on	Organ weights and	-clinical signs (coloured urine and	differences between the group	that ovary and uterus
(VOI. 3,	reduced bodyweight gain noted	adjusted body weight in	Taeces) (M, F)	mean uterus (and ovary) weight	weight of control and

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B.6.3.2.2/01)	in females at ≥10 mg/kg bw/day	control animals		of control and treated females	treated females are
	and in males at 30 mg/kg	remarkable higher than	<u>10 mg/kg bw/dag:</u>	at the terminal kill are	considered to reflect
OECD 409 (1998)	bw/day, changes in	in test item animals	-clinical signs (coloured urine and	considered to reflect differences	differences in the stage of
	haematological parameters	(statistical analysis not	faeces) (M, F)	in the stage of estrous cycle	estrous cycle between
Dog	(indicating haemolytic anaemia)	performed). Control	↓bw gain (F: 12% n.s.)	between individual animals and	individual animal and not
Beagle	noted in both sexes at $\geq 10 \text{ mg/kg}$	animals (two of four	$\downarrow$ FC (M)	not to be related to treatment.	to be related to treatment.
	bw/day, changes in biochemical	animals) showed estrous	-changes in haematological	No estrous cycle was	No estrous cycle was
M, F	parameters (indicating liver	cyclicity while treatment	parameters (\red blood cell	determined in vaginal tissue.	determined in treated
4/sex/dose	toxicity) noted in both sexes at	animals (12 animals) did	count (M, F), ↑reticulocyte count	Based on the available	animals but in control
	30 mg/kg bw/day, increased liver	not show activity.	(M, F), ↓mean cell haemoglobin	information it is not possible to	animals (2 of 4 animals).
GLP: Yes	weight (noted in females at $\geq 10$		concentration (M, F), ↑platelet	explain why only the control	The lack of cyclic activity
	mg/kg bw/day and in males at 30		count (F, n.s.), ↑platelet crit	animals show estrous cyclicity.	might be indicative of
Dose levels:	mg/kg bw/day), increased		(F, n.s.), ↑total white blood cell	An exogenous influence by an	endogenic activity.
0, 3, 10 and 30 mg/kg	thyroid/parathyroid weight noted		count (F, n.s.))	endocrine acting substance	
bw/day	in males at $\geq 10$ mg/kg bw/day,		-changes in organ weights	cannot be excluded, however if	
	increased spleen weight noted in		(†adjusted liver (F: 27%),	Quinoclamine would exhibit	
	females at 30 mg/kg bw/day),		↑adjusted thyroid/parathyroid (M:	endocrine activity additional	
	gross pathology changes noted in		33%))	effects should have been	
	females at 30 mg/kg bw/day		-histopathological changes in	observed in other organs within	
	(enlarged spleen, mottled liver		bone marrow (haemopoiesis (M,	this study, particularly	
	and red bladder) and		F)), liver (sinusoidal cell pigment	impairment of spermatogenesis	
	histopathological changes noted		characterised by presence of	and ovarian lesion which would	
	in the bone marrow (both sexes		intracytoplasmic iron-containing	have become visible during 90	
	at $\geq 10 \text{ mg/kg bw/day}$ ), liver		pigment (M, F)), urinary bladder	day of treatment.	
	(both sexes at ≥10 mg/kg		(cystitis (one female))		
	bw/day), urinary bladder (noted				
	in females at ≥10 mg/kg bw/day		<u>30 mg/kg bw/day:</u>		
	and in males at 30 mg/kg		-clinical signs (coloured urine and		
	bw/day), kidney (noted in both		faeces) (M, F)		
	sexes at 30 mg/kg bw/day) and		↓ <b>bw gain</b> (M: 31%, F: 35%)		
	spleen (noted in both sexes at 30		$\downarrow$ FC (M, F)		
	mg/kg bw/day)		-changes in haematological		
			parameters (\red blood cell		
			count (M, F), ↓haemoglobin		
			(M: 18%, F: 19%), ↓packed cell		
			volume (M, F), ↑reticulocyte		
			count (M, F), ↓mean cell		
			haemoglobin concentration (M,		
			F), ↑mean cell volume (M, F),		
			$\uparrow$ platelet count (M, F), $\uparrow$ platelet		

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		-			-
			crit (M, F), †total white blood cell count (M, F)) -changes in biochemistry (†mean total bilirubin (M, F)) -changes in organ weights (†adjusted liver (M: 20%, F: 29%), †adjusted thyroid/parathyroid (M: 32%), †adjusted spleen (F: 56% n.s.)) -macroscopic changes in spleen (enlarged two females), liver (mootled, one female) and urinary bladder (red, one female) -histopathological changes in bone marrow (haemopoiesis characterised by greater cellularity (M, F)), spleen (haemopoiesis characterised by increased haemopoietic cells in the red pulp (M, F), congestion of the splenic red pulp (M, F)), liver (sinusoidal cell pigment characterised by presence of intracytoplasmic iron-containing pigment (M, F)), urinary bladder (transitional cell hyperplasia (M, F), arteritis (one male), cystitis (one female))		
Long-term toxicity and carcinogenicity (RAR Vol. 3, B.6.5.1/01) Oral (dietary)	NOAEL for systemic toxicity was 4 ppm (corresponding to 0.21 and 0.28 mg/kg bw/day for males and females, respectively) based on reduced bodyweight gain noted in females at 676 ppm (38.3 mg/kg bw/day), changes in haematological parameters noted in both sexes at 676 ppm (37.6 and 38.3 mg/kg bw/day in males	52 ppm (3.65 mg/kg bw/day) Uterus: Hydrometra (at 26 weeks: 3 animals compared to 1 in control group)	<ul> <li><u>52 ppm:</u></li> <li>-changes in urinalysis</li> <li>(yellow/brown or orange discoloration) (M, F)</li> <li>-changes in organ weights (Week 27: ↑kidney (M: 8%))</li> <li>-histopathological changes in urinary bladder (epithelial hyperplasia (M, F), kidneys (epithelial hyperplasis (M, F),</li> </ul>	An increased number of females showing hydrometra were observed after 26 and 52 weeks of treatment. Principally hydrometra can be induced by estrogenic action, e.g. during permanent estrus in an age- dependent spontaneous disturbance of ovarian function. To discern whether hydrometra	Increased incidence of hydrometra was observed but did not show a clear relationship to treatment. Further estrogenic alterations such as ovarian atrophy, hyperplasia of vaginal and uterine tissue, testicular and prostate lesions were not presented.

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No guideline claims	and females, respectively),	676 ppm (49.4 mg/kg	↑ renal focal calcification (F),	was exogenously induced by	
presented in study	changes in biochemical	<u>bw/day)</u>	ureter (epithelial hyperplasia (M,	Quinoclamine or displays a	
report	parameters noted in both sexes at		F), lungs (arterial calcification	physiological phenomenon	
	676 ppm, changes in organ	Uterus:	(M))	could not be decided solely	
Rat	weights (increased kidney weight	Hydrometra		based on the presence of	
Crl:CD(SD)BR	noted in males at $\geq$ 52 ppm and in	(at 26 weeks: 4 animals	<u>676 ppm:</u>	hydrometra. However,	
	females at 676 ppm; increased	compared to 0 in control	-clinical signs (orange fur	considering the other endocrine	
50/sex/group	thyroid, thymus, heart and	group;	staining, ↓incidence of mass	sensitive reproductive organs,	
	adrenals noted in females at 676	at 52 weeks: 1 animal	bearing animals) (M, F)	further estrogenic alterations	
GLP: No	ppm), changes in urinalysis noted	compared to 0 in control	↓ <b>bw gain</b> (toxicology evaluation:	should become visible e.g.	
	in both sexes at ≥52 ppm (At 52	group)	F: 28%; carcinogenicity	ovarian atrophy, hyperplasia of	
Dose levels:	ppm and 676 ppm: yellow/brown		evaluation: F: 27%)	vaginal and uterine tissue,	
<b>Carcinogenicity</b>	to orange discoloration; At 676		$\downarrow$ FC (M, F)	testicular and prostate lesions.	
groups:	ppm: diuretic males),		-changes in haematological	The respective organs were	
0, 4, 52, 676 ppm	macroscopic changes noted in		parameters (\packed blood cell	concerning this matter	
corresponding to	both sexes at 676 ppm		volume (M week 27, 79; F week	unremarkable. Thus it is to	
0, 0.21, 2.82, 37.6	(discoloration in urinary bladder		53), ↓haemoglobin (M: 8% week	assume that observed	
mg/kg bw/day in	and skin) and histopathological		27, F 5% week 27, 9% week 53),	hydrometra within this study	
males and 0, 0.28,	changes noted in both sexes at		↓red blood cell count (M week 27,	was not due to exogenous	
3.65, 49.4 mg/kg	≥52 ppm.		79; F: week 27, 53))	endocrine influence.	
bw/day in females			-changes in biochemical		
	NOAEL for tumour incidence		parameters ( <i>†blood</i> urea nitrogen		
Chronic toxicology	was 52 ppm (corresponding to		(M n.s., F n.s.), ↓calcium (M:		
groups:	2.82 and 3.65 mg/kg bw/day in		week 27, 79; F: n.s.), ↓inorganic		
0, 4, 52, 676 ppm	males and females, respectively)		phosphorous (M: n.s, F: week 27,		
corresponding to 0,	based on benign transitional cell		53), ↓lactate dehydrogenase		
0.21, 2.89, 38.3	papillomas in urinary bladder		(M: week 79, 103; F: week 103))		
mg/kg bw/day in	and increased incidence of		-changes in organ weights		
males; 0, 0.28, 3.72,	benign phaeochromocytoma in		(Week 27: ↑rel kidney (M: 15%),		
51.5 mg/kg bw/day in	adrenals noted in both sexes at		↑adrenals (F: 38%), Week 53:		
females	676 ppm		†kidney (M: 10%), Week 79:		
			↑heart (M: 18%, F: 28%), ↑brain		
Study was checked			(F: 28%), ↑spleen (F. 13%),		
for compliance with			104: ↑kidney (F: 19%), Week 104		
OECD TG 453 and			↑brain (F: 23%), ↑thyroid		
following deviations			(F:43%), ↑(heart (F: 16%),		
were noted:			↑adrenals (F: 9%), ↑thymus (F:		
i. Haematological			50%))		
examination was not			-changes in urinalysis		
carried out at 3			(yellow/brown or orange		
months (the guideline					

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recommends			discoloration (M, F), diuretic		
measurements at 3			animals (M))		
months if effect was			-macroscopical changes in		
seen on			urinary bladder (orange		
haematological			discoloration of the urinary		
parameters in a			bladder serosa) (M, F) and skin		
previous 90 day			(orange staining (M, F))		
study)			-histopathological changes in		
ii. Prothrombin time			urinary bladder (benign		
and activated partial			transitional cell papilloma (M, F),		
thromboplastin time			epithelial hyperplasia (M, F)		
was not investigated			polyp (one female), chronic		
iii. Urea was not			inflammation (M. F), kidneys		
investigated			(epithelial hyperplasia (M, F).		
iv. Uterus and			renal papillary		
epididvmides were			degeneration/necrosis (M, F)		
not weighed			↑ renal cortical scarring (M, F)		
v. Coagulating gland.			pelvis polyp (one male). ↑ renal		
ileum, lacrimal gland			focal calcification, ureter		
and seminal vesicle			(epithelial hyperplasia (M, F).		
were not investigated			urethra (epithelial hyperplasia		
for history			(M F) adrenals (benign		
for instoputiology			phaeochromocytoma M F)		
			pancreas (^pancreatic acinar		
			atrophy (M E) parathyroid		
			(epithelial hyperplasia (M)		
			memmery gland (memmery		
			acinar development and secretion		
			(E) lungs (arterial calcification		
			$(\mathbf{F})$ , lungs (alternal calcification) $(\mathbf{M}, \mathbf{E})$ overing (look of evolution)		
			(W, F), Ovaries (lack of cyclic		
			activity))		
					1
Mammary gland			1	1	
Long-term toxicity	NOAEL for systemic toxicity	<u>676 ppm (49.4 mg/kg</u>	<u>676 ppm:</u>	After 104 weeks of treatment	Reduced mammary acinar
and carcinogenicity	was 4 ppm (corresponding to	<u>bw/day)</u>	-clinical signs (orange fur	there was a significant	development and secretion
	0.21 and 0.28 mg/kg bw/day for		staining, ↓incidence of mass	reduction in mammary tumors	were noted in females at a
(RAR Vol. 3,	males and females, respectively)	Mammary gland,	bearing animals) (M, F)	and reduced mammary acinar	dose level with lower food
B.6.5.1/01)	based on reduced bodyweight	females:		development and secretion in	consumption and reduced
	gain noted in females at 676 ppm			the high dose females compared	body weight, thus this

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Oral (dietary)	(38.3 mg/kg bw/day), changes in	mammary acinar	↓ <b>bw gain</b> (toxicology evaluation:	to control. As stated by the	effect might be caused by
	haematological parameters noted	development and	F: 28%; carcinogenicity	study authors, this was	bad health condition.
No guideline claims	in both sexes at 676 ppm (37.6	secretion reduced	evaluation: F: 27%)	probably related with the lower	
presented in study	and 38.3 mg/kg bw/day in males		$\downarrow$ FC (M, F)	food consumption and reduced	
report	and females, respectively),		-changes in haematological	body weight observed in the	
	changes in biochemical		parameters (\packed blood cell	same females	
	parameters noted in both sexes at		volume (M week 27, 79; F week		
Rat	676 ppm, changes in organ		53), ↓haemoglobin (M: 8% week		
Crl:CD(SD)BR	weights (increased kidney weight		27, F 5% week 27, 9% week 53),		
	noted in males at $\geq$ 52 ppm and in		$\downarrow$ red blood cell count (M week 27,		
50/sex/group	females at 676 ppm; increased		79; F: week 27, 53))		
	thyroid, thymus, heart and		-changes in biochemical		
GLP: No	adrenals noted in females at 676		parameters ( <i>fblood</i> urea nitrogen		
	ppm), changes in urinalysis noted		(M n.s., F n.s.), ↓calcium		
Dose levels:	in both sexes at $\geq$ 52 ppm (At 52		(M: week 27, 79; F: n.s.),		
Carcinogenicity	ppm and 676 ppm: yellow/brown		↓inorganic phosphorous (M: n.s,		
groups:	to orange discoloration; At 676		F: week 27, 53), <i>lactate</i>		
0, 4, 52, 676 ppm	ppm: diuretic males),		dehydrogenase (M: week 79, 103;		
corresponding to	macroscopic changes noted in		F: week 103))		
0, 0.21, 2.82, 37.6	both sexes at 676 ppm		-changes in organ weights		
mg/kg bw/day in	(discoloration in urinary bladder		(Week 27: ↑rel kidney (M: 15%),		
males and 0, 0.28,	and skin) and histopathological		↑adrenals (F: 38%), Week 53:		
3.65, 49.4 mg/kg	changes noted in both sexes at		↑kidney (M: 10%), Week 79:		
bw/day in females	≥52 ppm.		↑heart (M: 18%, F: 28%), ↑brain		
5			(F: 28%), ↑spleen (F. 13%),		
Chronic toxicology	NOAEL for tumour incidence		↑kidney (F: 19%), Week 104:		
groups:	was 52 ppm (corresponding to		↑brain (F: 23%), ↑thyroid		
0, 4, 52, 676 ppm	2.82 and 3.65 mg/kg bw/day in		(F:43%), ↑(heart (F: 16%),		
corresponding to 0,	males and females, respectively)		↑adrenals (F: 9%), ↑thymus (F:		
0.21, 2.89, 38.3	based on benign transitional cell		50%))		
mg/kg bw/day in	papillomas in urinary bladder		-changes in urinalysis		
males; 0, 0.28, 3.72,	and increased incidence of		(yellow/brown or orange		
51.5 mg/kg bw/day in	benign phaeochromocytoma in		discoloration (M, F), diuretic		
females	adrenals noted in both sexes at		animals (M))		
	676 ppm		-macroscopical changes in		
Study was checked			urinary bladder (orange		
for compliance with			discoloration of the urinary		
OECD TG 453 and			bladder serosa) (M, F) and skin		
following deviations			(orange staining (M, F))		
were noted:			-histopathological changes in		
			urinary bladder (benign		

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i Haematological	transitional cell papilloma (M F)
examination was not	enithelial hypernlasia (M. F)
carried out at 3	polyn (one female), chronic
months (the guideline	inflamation (M, E) kidnaws
montais (the guidenne	(anithalia) (W, F), <u>Nulleys</u>
recommends	(epinenai hyperpiasia (M, F),
measurements at 5	renai papinary
months if effect was	degeneration/necrosis (M, F)
seen on	renal cortical scarring (M, F)
haematological	pelvis polyp (one male), ↑ renal
parameters in a	focal calcification, <u>ureter</u>
previous 90 day	(epithelial hyperplasia (M, F),
study)	<u>urethra (</u> epithelial hyperplasia (M,
ii. Prothrombin time	F)), <u>adrenals</u> (benign
and activated partial	phaeochromocytoma M, F),
thromboplastin time	pancreas (†pancreatic acinar
was not investigated	atrophy (M, F), <u>parathyroid</u>
iii. Urea was not	(epithelial hyperplasia (M),
investigated	<u>mammary gland</u> (↓mammary
iv. Uterus and	acinar development and secretion
epididymides were	(F)), lungs (arterial calcification
not weighed	(M, F), ovaries (lack of cyclic
v. Coagulating gland.	activity))
ileum, lacrimal gland	
and seminal vesicle	
were not investigated	
for historiathology	
lor instopution 6,	

# Table 2.6.8.3-02: Effects on reproduction and development

Study	NOAEL in study	Effect on reproduction	Other effects at the dose level of effect on reproduction	Comments by study author	Comments by RMS			
Reduced litter size/post-implantation loss/foetal weight								
Two generation	The NOAEL for parental animals was set	<u>500 ppm:</u>	<u>500 ppm:</u>	The lower	Reduced litter			
reproduction study	at 25 ppm (1.6 mg/kg bw/day) based on	Reduced litter size in	Parental:	implantation	size was noted at			
	clinical signs (hunched posture) noted in	F2a and F2b	-clinical signs (F0/F1: hunched posture)	efficiency (increased	a dose level with			
(RAR Vol. 3,	P1 and P2 generation animals at 500 ppm	generations (mean	↓ <b>bw</b> (P1 M: 4%; P2 M: 10%; P2 F 10%)	pre-implantation loss	parental toxicity			
B.6.6.1/01)	(37 mg/kg bw/day), reduced body weight	litter size born in F2a	↓ <b>bw gain</b> (P1 M: 7%, P2 M: 11%; P2 F: 9%)	and decreased fetal				

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	noted in P2 males and females at 500 ppm,	generation: 4 males	↓litter size in F2a and F2b generations (mean	viability) were not	
In-house method	and reduced bodyweight gain noted in P2	and 5 females	litter size born in F2a generation: 4 males and	noted in the F1	
	males at 500 ppm.	compared to 6 males	5 females compared to 6 males and 6 females	generation and	
Rat		and 6 females in the	in the control group; mean litter size born in	therefore not	
Sprague-Dawley	The NOAEL for offsprings was set at 25	control group: mean	F2b generation: 5 males and 5 females	considered to be	
1 8	ppm (1.6 mg/kg bw/day) based on reduced	litter size born in F2b	compared to 7 males and 6 females in control	treatment related	
M. F	body weights at weaning in all filial	generation: 5 males	group)		
25/sex/group	generations noted at 500 ppm (37 mg/kg	and 5 females	group)		
25/Sex/group	bw/day) and gray lung cysts in P?	compared to 7 males	Offenring:		
GLP: No	offspring reared for 3 months	and 6 females in	-clinical signs (orange stained fur F2b		
OEI : NO	onspring reared for 5 months.	and o ternates in	offenring)		
	The NOAEL for reproductive toxicity was	control group)	1  bw during last tion (E1a; 120) and 70) in		
De es lavela	The NOAEL for reproductive toxicity was		<b>UN</b> utiling factation (F1a, 15% and 7% in		
Dose levels:	set at 500 ppm (57 mg/kg bw/day).		males and remaines, respectively, F10: 14%		
0, 1, 25, 500 ppm			E212 8% and 0% in males and females, respectively;		
Corresponding to:			F2a: 8% and 9% in males and remains,		
F0: 0, 0.07, 1.6, 30.9			respectively; F2b: 11% and 5% in males and		
mg/kg bw/day in males;			females, respectively)		
0, 0.08, 1.9 and 37.7			Ulitter size in F2a and F2b generations (mean		
mg/kg bw/day in			litter size born in F2a generation: 4 males and		
females			5 females compared to 6 males and 6 females		
F1: 0, 0.07, 1.7 and			in the control group; mean litter size born in		
37.0 mg/kg bw/day in			F2b generation: 5 males and 5 females		
males; 0, 0.08, 2.0 and			compared to 7 males and 6 females in control		
43.8 mg/kg bw/day in			group)		
females			-increased incidence of gray lung cysts in		
			F2b offspring reared for 3 months (39		
			compared to 11 in control group)		
Study was checked for					
compliance with OECD					
TG 416 (2001) and					
following deviations					
were noted:					
i. No evaluation of the					
oestrus cycles was					
performed for either					
generation					
ii. No examination of					
sperm parameters was					
performed for either					
generation					
M, F 25/sex/group GLP: No Dose levels: 0, 1, 25, 500 ppm corresponding to: F0: 0, 0.07, 1.6, 30.9 mg/kg bw/day in males; 0, 0.08, 1.9 and 37.7 mg/kg bw/day in females F1: 0, 0.07, 1.7 and 37.0 mg/kg bw/day in males; 0, 0.08, 2.0 and 43.8 mg/kg bw/day in females Study was checked for compliance with OECD TG 416 (2001) and following deviations were noted: i. No evaluation of the oestrus cycles was performed for either generation ii. No examination of sperm parameters was performed for either generation	body weights at weaning in all filial generations noted at 500 ppm (37 mg/kg bw/day) and gray lung cysts in P2 offspring reared for 3 months. The NOAEL for reproductive toxicity was set at 500 ppm (37 mg/kg bw/day).	generation: 5 males and 5 females compared to 7 males and 6 females in control group)	group) <u>Offspring:</u> -clinical signs (orange stained fur F2b offspring) ↓ <b>bw</b> during lactation (F1a: 13% and 7% in males and females, respectively; F1b: 14% and 9% in males and females, respectively; F2a: 8% and 9% in males and females, respectively; F2b: 11% and 5% in males and females, respectively) ↓ <b>litter size</b> in F2a and F2b generations (mean litter size born in F2a generation: 4 males and 5 females compared to 6 males and 6 females in the control group; mean litter size born in F2b generation: 5 males and 5 females compared to 7 males and 6 females in control group) <b>-increased incidence of gray lung cysts</b> in F2b offspring reared for 3 months (39 compared to 11 in control group)		

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iii. Gestation length was not specified iv. organs were not weighed v. Vagina, testis, epididymides, seminal vesicles, prostate and coagulating gland were not investigated microscopically vi. Detailed testicular histopathology was not performed vii. Postlactational ovary (primordial and growing follicles) histopathology was not performed viii. For the offspring, age at vaginal opening or PPS for the F1 and F2 was not determined	Study is a range finding study. Due to low	200 mg/kg bw/day:	Maternal effects:	Maternal toxicity:	Increased
finding study (Vol 3, B.6.6.2.1/01)	number of animals used in the study it is not considered appropriate to establish a NOAEL/LOAEL	-increased incidence of post-implantation loss (24.5% compared to 2.4% in controls)	8 mg/kg bw/day: No treatment-related effects 50 mg/kg bw/day: -clinical signs (staining around eye)	body weight loss and reduced food consumption noted at 80 mg/kg bw/day (at start of dosing)	incidence of post- implantation loss and reduced foetal weight were noted at a
No guideline claimed in study		-reduced foetal weight (27%)	80 mg/kg bw/day: -clinical signs (stained urine, stained fur		dose level with marked maternal toxicity
Rat Crl:CD (SD) BR			around head) - bw loss/↓bw gain (day 7-10: -3.5 g, day 10- 13: 14% (n,s))		
F			FC (Pregnancy Days 7-10: 27% Pregnancy		
5/group			Days 10-13: 20%, Pregancy Days: 13-17: 17%)		
GLP: Yes			-macroscopic changes (enlarged spleen in one female)		
Dose levels:					

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0, 8, 50, 80, 200, 500 mg/kg bw/day	200 mg/kg bw/day: -mortality (one animal died, two animals
	were killed in extremis)
Vehicle: 0.25% gum	-clinical signs (lethargy, hunched posture,
tragacanth	piloerection, stained urine, soft stained
	faces, stained fur around anus, vagina, head)
Gestation Days 7-17	- <b>bw loss/ bw gain</b> (day 7-10: -19.8 g. day
	10-13:-1.5 g. day 13-17: 42% (n s.))
	FC (Pregnancy Days 7-10: 52%, Pregnancy
	Days 10-13: 43% Pregancy Days: 13-17:
	29%)
	-macrosconic changes (enlarged spleen and
	adranals, arosion of the stomach mucosa)
	t next implantation loss (24.5% compared
	to 2.4% in contractor
	500 mg/kg hu/dau
	montality (one seimed died en deu 10 of
	-more than the dama died of day 10 of
	bills d in partemining 10 m a 11 m as were
	killed in extremis on days 10 or 11 of
	pregnancy)
	-clinical signs (lethargy, hunched posture,
	piloerection, stained urine, soft stained
	faeces, stained fur around anus, vagina, head)
	- <b>bw loss</b> (-34 g, day 7-10)
	↓FC
	Developmental effects:
	<u>8 mg/kg bw/day:</u>
	No treatment-related effects
	50 mg/kg bw/day:
	No treatment-related effects
	80 mg/kg bw/day:
	↓mean foetal weight (8% n.s.)
	<u>200 mg/kg bw/day:</u>
	↑ <b>postimplantation loss</b> (24.5% compared to
	2.4% in controls)

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			↓mean foetal weight (27%)		
Teratology study	NOAEL for maternal toxicity was 5 mg/kg	75 mg/kg bw/day:	Maternal effects:	The growth	Reduced foetal
	bw/day based on reduced bodyweight gain	Reduced foetal		retardation (reduced	weight was noted
(Vol 3, B.6.6.2.1/02)	(25%) noted in dams at 75 mg/kg bw/day	weight (7%)	5 mg/kg bw/day:	foetal weight) is most	at a dose level
	and changes in gross pathology (enlarged		No treatment related effects	probably due to	with maternal
No guideline claimed in	spleen) noted in dams at ≥20 mg/kg			reduced maternal	toxicity
study	bw/day.		<u>20 mg/kg bw/day:</u>	bodyweight)	
			-macroscopic changes (enlarged spleen, one		
Rat	NOAEL for developmental toxicity was 5		dam)		
Crl:CD (SD) BR	mg/kg bw/day based on reduced foetal				
	weight (7%) noted at 75 mg/kg bw/day and		$\frac{75 \text{ mg/kg bw/day:}}{100000000000000000000000000000000000$		
F	increased incidence of aortic abnormalities		- <b>bw gain</b> (25% day $7-17$ )		
24/group	and skeletal variations noted at $\geq 20 \text{ mg/kg}$		$\downarrow$ FC (Gestation Days /-10: 25%, Gestation Days 10, 12: 14%)		
CI D: Vos	bw/day.		Days 10-13. 14%)		
OLI. IES			4/24 dams)		
Dose levels:			4/24 dams)		
0.5.20 and 75 mg/kg			Developmental effects:		
bw/day			5 mg/kg bw/day:		
			No treatment-related effects		
Vehicle: 0.25% gum					
tragacanth			<u>20 mg/kg bw/day:</u>		
			-abnormalities (innominate artery absent,		
Gestation Days 7-17			one foetus)		
			-increased incidence of skeletal variants		
The study was checked			(skull: hyoid not ossified; vertebrae: thoracic		
for compliance with			centre one or more bilobed)		
OECD TG 414 and					
following deviations			$\frac{15 \text{ mg/kg bw/day:}}{16 \text{ scale main left}}$		
i Europeuno timo in			ploetal weight (7%)		
1. Exposure time in			four footuses: situs inversus, two footuses:		
hetween days 7 and 17			interrupt aortic arch one foetus)		
of pregnancy (the			-increased incidence of skeletal variants		
guideline is not			(skull: hvoid not ossified: vertebrae: thoracic		
intended to examine			centre one or more bilobed/bipartite:		
solely the period of			sternebrae: 5th and 6th sternebrae not		
organogenesis (e.g.			ossified, one or more bilobed, bipartite or		
days 5-15 in the rodent)			misaligned)		

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but also effects from preimplantation, when appropriate, through the entire period of gestation to the day before caesarean section) ii. Treatment was not extended (the guideline states: If preliminary studies, when available, do not indicate a high potential for preimplantation loss, treatment may be extended to include the entire period of gestation, from mating to the day prior to scheduled kill) iii. The choice of vehicle was not justified in study report					
Teratology range finding study (RAR Vol. 3,	Study is a range finding study. Due to low number of animals used in the study it is not considered appropriate to establish a NOAEL/LOAEL	50 mg/kg bw/day: -increased post- implantation loss (6.2% compared to	Maternal effects: 10 mg/kg bw/day: ↓ <b>bw gain</b> (18%) (Day 6-20)	It is stated by the study author that the reduced fetal weight is due to the reduced	Reduced fetal weight and increased post- implantation loss
В.0.0.2.1/03)		2.8% in controls,	$\frac{50 \text{ mg/kg bw/day:}}{100000000000000000000000000000000000$	maternal body weight	were noted at
NT. 111 1.1 1.1		mainly due to three	$\downarrow$ <b>bw gain</b> (2/%) (Day 6-20)	gain and food	dose levels with
No guideline claimed in study		deaths in one litter)	↓FC (Days 4-20: 14%, Days 6-19: 14%, Days 19-20: 48%)	consumption	maternal toxicity
		<u>100 mg/kg bw/day:</u>	↑postimplantation loss (6.2% compared to		
Rat		-increased post-	2.8% in controls, mainly due to three deaths		
Crl:CD (SD) IGSBR		implantation loss	in one litter)		
		(10.7% compared to	↑number of early intrauterine deaths (mean		
F		2.8% in controls)	number: 1.0 compared to 0.4 in control)		

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7/group	-reduced litter size	mean litter weight (2%)	
·· 8F	(12  compared to  126)	φ	
CLD V		100 / 1 / 1	
GLP: Yes	in control)	100 mg/kg bw/day:	
		↓ <b>bw gain</b> (41%) (Day 6-20)	
Dose levels:		↓FC (Days 4-20: 21%), Days 6-19: 21%,	
0, 10, 50, 100 mg/kg		Days 19-20: 30%)	
hw/day		gravid uterus weight (17%)	
o m du j		↑ nestimulantation loss (10.7% compared to	
		postimpiantation loss (10.7% compared to	
venicie: 1% aqueous		2.8% in controls)	
methylcellulose		<b>↑number of early intrauterine deaths</b>	
		(mean number: 1.2 compared to 0.4 in	
Gestation Days 6-19		control)	
		mean litter weight (16%)	
		mean litter size (12 compared to 12 6 in	
		aontrol)	
		control	
		Developmental effects:	
		10 mg/kg bw/day:	
		mean foetal weight (8%)	
		Thean Idetai Weight (070)	
		50	
		<u>50 mg/kg bw/day:</u>	
		↓mean foetal weight (11%)	
		<b>↑postimplantation loss</b> (6.2% compared to	
		2.8% in controls, mainly due to three deaths	
		in one litter)	
		↑number of early intrauterine deaths	
		(mean number: 1.0 compared to 0.4 in	
		(incar number, 1.0 compared to 0.4 III	
		↓mean litter weight (2%)	
		<u>100 mg/kg bw/day:</u>	
		↓mean foetal weight (12%)	
		<b>†nostimplantation loss</b> (10.7% compared to	
		2.8% in control)	
		2.070 m control)	
		number of early intrauterine deaths	
		(mean number: 1.2 compared to 0.4 in	
		control)	
		<b>↓mean litter weight</b> (16%)	

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			$\downarrow$ mean litter size (12 compared to 12.6 in		
			control)		
Teratology study	NOAEL for maternal toxicity was 5 mg/kg	75 mg/kg bw/day:	Maternal effects:	Lower foetal weight	Reduced litter
	bw/day based on reduced bodyweight gain	-reduced litter size	5 mg/kg bw/day:	was associated by the	size and increased
(RAR Vol. 3,	noted in dams at $\geq 20 \text{ mg/kg bw/day, body}$	(12 compared to 14.8	No treatment-related effects	authors with the	post-implantation
B.6.6.2.1/04)	weight loss noted in dams at 75 mg/kg	in control)		significantly lower	loss (n.s.) were
	bw/day, reduced mean gravid uterus	-increased post-	20 mg/kg bw/day:	maternal weight	noted at a dose
No guideline claimed in	weight noted in dams at $\geq 20 \text{ mg/kg}$	implantation loss	-clinical signs (paddling of the forelimbs	gains.	level with
study	bw/day, reduced mean litter weight noted	(11% compared to	from Day 14 of gestation)		maternal toxicity.
	at $\geq 20 \text{ mg/kg bw/day}$ , increased number of	5% in control, n.s.)	↓ <b>bw gain</b> (Days 7-8: 62%, Days 17-19: 21%)	The increased	
Rat	post-implantation loss and early	-reduced foetal	↓FC (Days 7-8: 14%, Days 9-12: 17%,	incidence of post-	
Crl:CD (SD) IGSBR	intrauterine deaths noted at 75 mg/kg	weight (12%)	Days 12-15: 10%, Days 15-17: 12%,	implantation loss	
	bw/day, and reduced mean litter size noted		Days 17-19: 12%)	might be due to	
F	at 75 mg/kg bw/day.		↓mean gravid uterus weight (15%)	unfavourable study	
24/group			↓mean litter weight (13%)	conditions (the rats	
	NOAEL for developmental toxicity was 5			were supplied time-	
GLP: Yes	mg/kg bw/day based on reduced foetal		<u>75 mg/kg bw/day:</u>	mated)	
	weight noted at $\geq 20 \text{ mg/kg bw/day}$ ,		-clinical signs (paddling of the forelimbs		
The study was checked	increased number of post-implantation loss		from Day 10, nose rubbing)		
for compliance with	and early intrauterine deaths noted at 75		↓ <b>bw gain</b> (Days 17-19: 41%)		
updated OECD TG 414	mg/kg bw/day, reduced mean litter size		<b>-bw loss</b> (Days 6-7: -4.6 g, Days 7-8: -2.6 g,		
(2001) and following	noted at 75 mg/kg bw/day, increased		Days 8-9: -0.4 g)		
deviations were noted:	incidence of skeletal variations noted at		↓FC (Days 4-6: 9%, Days 6-7: 27%,		
<i>i. Exposure time in</i>	$\geq 20 \text{ mg/kg bw/day, and malformations}$		Days 7-8: 44%, Days 8-9: 34%,		
study was once daily	noted at 75 mg/kg bw/day.		Days 9-12: 30%, Days 12-15: 17%,		
between days 6 and 19			Days 15-17: 13%, Days 17-19: 33%)		
of pregnancy (the			↓mean gravid uterus weight (30%)		
guideline is not			↑post-implantation loss (11% compared to		
intended to examine			5% in control, n.s.)		
solely the period of			↑ number of early intrauterine deaths		
organogenesis (e.g.			(1.1 compared to 0.7 in control)		
aays 5-15 in the rodent)			$\downarrow$ mean litter size (12 compared to 14.8 in		
but also effects from			control)		
preimplantation,			↓mean litter weight (29%)		
when appropriate,			Developmental effectes		
through the entire			Developmental effects:		
period of gestation to			5 mg/kg hyv/davy		
ine day before			<u>S mg/kg bW/day:</u> No treatment related offects		
cuesurean section)			no neannent-related effects		

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ii. Treatment was not extended (the guideline states: If preliminary studies, when available, do not indicate a high potential for preimplantation loss, treatment may be extended to include the entire period of gestation, from mating to the day prior to scheduled kill) iii. The choice of vehicle was not justified in study report <u>Dose levels:</u> 0, 5, 20, 75 mg/kg bw/day Vehicle: 1% aqueous methylcellulose			20 mg/kg bw/day: ↓foetal weight (7%) ↓mean litter weight (13%) ↑incidence of skeletal variations (incomplete ossification of skull bone (frontal and nasal) and unossified fifth sternebrae) 75 mg/kg bw/day: ↓foetal weight (12%) ↓litter weight (29%) ↑post-implantation loss (11% compared to 5% in control) ↑pre-implantation loss (17.4% compared to 8.6% in control but within current background data) ↑number of early intrauterine deaths (1.1 compared to 0.7 in control) ↓mean litter size (12 compared to 14.8 in control) ↑incidence of skeletal variations (incomplete ossification of skull bone (frontal and nasal) and unossified fifth sternebrae) -malformations (subcutaneous oedema (one		
Gestation Days 6-19			foetus), kidney misshapen (one foetus),		
		20 / 1 / 1	hydropnephrosis (three foetuses))		T 1
finding study	Study is a range finding study. Due to low number of animals used in the study it is	<u>20 mg/kg bw/day:</u> -increased post-	<u>Maternal effects:</u> 8 mg/kg bw/day:	There is no explanation given by	increased
intering steady	not considered appropriate to establish a	implantation loss	No treatment-related effects	the study author with	implantation loss
$(RAR Vol. 3, P \in (2.2)(01))$	NOAEL/LOAEL	(31.1 compared to	20 mg/kg hu/dayu	respect to the	was noted.
<b>D.0.0.2.2/01</b> )		8.7 III control)	20 mg/kg bw/day: ↑post-implantation loss (31.1 compared to	post-implantation	not be explained
No guideline claimed in		50 mg/kg bw/day:	8.7 in control)	loss. There was no	by maternal
study		-increased post-	50 mg/kg bw/day:	growth retardation	toxicity
Rabbit		(61.0 compared to	-clinical signs (coloured urine)	surviving foetuses	
New Zealand White		8.7 in control)	↓bw (Day 10: 4%, Day 14: 5%)	indicating severe	
F		80/8 mg/kg hw/day.	↓FC (days 6-10) ↑ <b>nost-implantation loss</b> (61.0 compared to	maternal toxicity	
5/group		ooro mg/ng o mauy.	8.7 in control)		

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GLP: Yes <u>Dose levels:</u> 0, 8, 20, 50, 80/8a, 200/20a, 500/50a Vehicle: 0.25% gum tragacanth Gestation Days 6-18	-increased post- implantation loss (25.0 compared to 8.7 in control) <u>200/20 mg/kg</u> <u>bw/day:</u> -increased post- implantation loss (30.0 compared to 8.7 in control)	80/8 mg/kg bw/day:         -clinical signs (coloured urine)         ↓bw (Day 7: 4%, Day 8: 3%, Day 10: 4%)         ↓FC (n.s.)         ↑ post-implantation loss (25.0 compared to 8.7 in control)         200/20 mg/kg bw/day:         -clinical signs (coloured urine)         ↓bw (Day 7: 6%, Day 10: 6%)         ↓FC (Day 6-10: 80%)         ↑ post-implantation loss (30.0 compared to 8.7 in control)         500/50 mg/kg bw/day:         -mortality (both animals died, one died on day 9 and the other on day 10 of pregnancy)         -clinical signs (lethargy, hunched posture, dark coloured urine)         ↓bw (Day 8: 12%)         ↓FC (Day 6-10: 80%)         Developmental effects:         8 mg/kg bw/day:         No treatment related effects         20 mg/kg bw/day:         ↑ post-implantation loss (31.1 compared to 8.7 in control)         -malformations (spina bifida, two animals, interrupted aortic arch major, one animal, hindlimb left malrotated, one animal)	
		50 mg/kg bw/day: ↑post-implantation loss (61.0 compared to 8.7 in control) -malformations (interrupted aortic arch major, one animal, kidney left agenesis, one animal)	

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			$\frac{80 \text{ mg/kg bw/day:}}{100000000000000000000000000000000000$		
			<b>†post-implantation loss</b> (25.0 compared to		
			8. / in control)		
			200/20 mg/kg by/day:		
			200/20 mg/kg bw/day:		
			<b>Post-inplantation loss</b> (50.0 compared to		
Teratology study	NOAEL for maternal toxicity was 22.5	<u>22.5 mg/kg bw/day:</u>	Maternal effects:	Maternal toxicity:	Reduced foetal
	mg/kg bw/day.	-reduced foetal	2.5  mg/kg bw/day:	body weight loss and	weight was not
(RAR Vol. 3,		weight (5% n.s.)	No treatment-related effects	reduced body weight	statistically
B.6.6.2.2/02)	NOAEL for developmental toxicity was			gain at 22.5 mg/kg bw	significant
<b>NT</b>	7.5 mg/kg bw/day based on increased		7.5 mg/kg bw/day:	(until day 9 of	reduced.
No guideline claimed in	foetal variations (increased number of		No treatment-related effects	pregnancy; afterwards	
study	caudal centra $\leq 15$ ) noted at 22.5 mg/kg		22.5	no differences to	
Dabbit	bw/day and mailormations noted at 22.5		$\frac{22.5 \text{ mg/kg bw/day:}}{1  bw gain (Day 6.0) 0 kg compared to 0.08 kg$	control)	
New Zeeland White	nig/kg bw/day.		in control Days 0.28:5%	It is stated by the	
New Zealand White			III control, Days 0-28. 5%)	study author that the	
F				retardation of fetal	
16/group			Developmental effects:	growth was most	
10/group			2.5 mg/kg bw/day:	probable a	
GLP: Yes			No treatment related effects	consequence of the	
				maternal toxicity	
			7.5 mg/kg bw/day:	observed	
Dose levels:			No treatment-related effects		
0, 2.5, 7.5, 22.5 mg/kg					
bw/day			<u>22.5 mg/kg bw/day:</u>		
-			↓foetal weight (5% n.s.)		
Vehicle: 0.25% gum			↑increased incidence of skeletal variants		
tragacanth			(increased no. of caudal centra ≤15 (84.9%		
			compared to 59.9% in control))		
Gestation Days 6-18			-malformations (scoliosis, one animal,		
			spina-bifida, three animals, anomalies of the		
The study was checked			aortic arch, two animals, sternebral fusions,		
for compliance with			three animals, hyperextension of limb or		
updated OECD TG 414			paw, one animal)		
(2001) and following					
deviations were noted:					
<i>i. Treatment was not</i>					
extended (the guideline					

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states: If preliminary studies, when available, do not indicate a high potential for preimplantation loss, treatment may be extended to include the entire period of gestation, from mating to the day prior to scheduled kill) ii. During the course of study relative humidity was within the range 54-76% (the guideline recommends the relative humidity not to exceed 70% other than during room cleaning) iii. The choice of vehicle was not justified in study report					
Teratology range finding study No guideline claimed in study Rabbit Crl.NZW/Kbl BR F 7/group GLP: Yes Dose levels: 0, 5, 17.5, 30 mg/kg	Study is a range finding study. Due to low number of animals used in the study it is not considered appropriate to establish a NOAEL/LOAEL	<u>30 mg/kg bw/day:</u> -increased incidence of post-implantation loss (22.4% compared to 14.9% in control) -reduced foetal weight (3%)	Maternal effects:         5 mg/kg bw/day:         No treatment related effects         17.5 mg/kg bw/day:         ↓ bw change (Days 7-28: 12% of controls)         ↓ FC         30 mg/kg bw/day:         -abortion (one animal, on Day 29)         ↓ bw change (Days 7-28: 10% of controls)         ↓ FC (Days 7-28: 2.4%, Days 28-29: 4%)         ↑ post-implantation loss (22.4% compared to 14.9% in control)         ↑ number of late intrauterine deaths (1.6 compared to 1.0 in control)         ↓ mean litter weight (6%)	It is stated by the study author that the reduced fetal weight is due to maternal body weight loss and reduced food consumption The increased incidence of post- implantation loss might be due to unfavourable study conditions (the rabbits were supplied time- mated, transported and had a very short acclimatization period	Increased incidence of post- implantation loss and reduced foetal weight were noted at a dose level with maternal toxicity
Dose levels: 0, 5, 17.5, 30 mg/kg bw/day			compared to 1.0 in control) ↓mean litter weight (6%)	and had a very short acclimatization period	

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Vehicle: 1% aqueous methylcellulose			Developmental effects: <u>5 mg/kg bw/day:</u> No treatment-related effects	before the start of dosing)	
Gestation Days 7-28			<u>17.5 mg/kg bw/day:</u> No treatment related effects		
			30 mg/kg bw/day: -abortions (one animal, on Day 29) ↑post-implantation loss (22.4% compared to 14.9% in control) ↑number of late intrauterine deaths (1.6 compared to 1.0 in control) ↓mean litter weight (6%) ↓mean foetal weight (3%)		
Teratology study	NOAEL for maternal toxicity was 5 mg/kg bw/day based on reduced bodyweight	<u>17.5 mg/kg bw/day:</u> - reduced mean litter	<u>Maternal effects:</u> <u>5 mg/kg bw/day:</u>	The increased incidence of post-	Increased incidence of post-
(RAR Vol. 3,	growth noted at 17.5 mg/kg bw/day	size (8.4 foetuses per	No treatment related effects	implantation loss	implantation loss
B.6.6.2.2/04)	(bodyweight change Days 12-15: 67% of	female compared to		might be due to	and reduced mean
	control) and 30 mg/kg bw/day (bodyweight	9.5 in control)	17.5 mg/kg bw/day	unfavourable study	litter size was
OECD 414	change Days 4-29: 46% of control),	,	<b>bw change</b> (bw change Days 12-15: 67% of	conditions (the rabbits	noted at a dose
	reduced mean litter size noted at $\geq 17.5$	30 mg/kg bw/day:	control)	were supplied time-	level with
Rabbit	mg/kg bw/day, increased post-implantation	-increased post-	mean litter size (8.4 foetuses per female	mated, transported	maternal toxicity
Crl.NZW/Kbl BR	loss noted at 30 mg/kg bw/day, increased	implantation loss	compared to 9.5 in control)	and had a very short	
	early and late intrauterine deaths noted at	(%/No. of affected		acclimatization period	
F	30 mg/kg bw/day, and reduced litter	dams: 24.9/13		before the start of	
24/group	weight noted at 30 mg/kg bw/day.	compared to 4.8/10	30 mg/kg bw/day:	dosing)	
		in control)	-mortality (one female killed on Day 18 of	The study author	
GLP: Yes	NOAEL for developmental toxicity was 5	- reduced mean litter	gestationc)	concluded that the	
	mg/kg bw/day based on reduced mean	size (7.8 foetuses per	↓bw (Days 4-29: 7%)	increased incidence of	
The study follows	litter size noted at $\geq 17.5$ mg/kg bw/day,	female compared to	<b>bw change</b> (Days 12-15: 0 kg compared to	intrauterine deaths is	
OECD TG 414 except	increased post-implantation loss noted at	9.5 in control)	0.12 kg in control, Days 4-29: 46% of	a result of the mild	
for following	30 mg/kg bw/day, increased early and late		control)	maternal toxicity at	
deviations:	intrauterine deaths noted at 30 mg/kg		↓FC	30 mg/kg bw/day	
i. Dosing of animals	bw/day, reduced litter weight noted at 30		<b>↑post-implantation loss</b> (%/No. of affected		
started on Day 7 of	mg/kg bw/day, increased incidence of		dams: 24.9/13 compared to 4.8/10 in control)		
gestation (the guideline	specific foetal variations noted at 30 mg/kg		<b>↑early intrauterine deaths</b> (1.0 compared to		
recommends	bw/day, and malformations noted at $\geq 17.5$		0.2 in control)		
administration to start	mg/kg bw/day.		<b>†late intrauterine deaths</b> (1.4 compared to		
on Day 6 of gestation)			0.3 in control)		
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u. During the course of	<b>thean litter size</b> (7.8 foctuses per female
study relative humidity	compared to 9.5 in control)
was within the range	↓litter weight (24%)
30-80% (the guideline	
recommends the	Developmental effects:
relative humidity not to	5 mg/kg bw/day:
exceed 70% other than	No treatment related effects
during room cleaning)	
iii. The choice of	17.5 mg/kg bw/day:
vehicle was not justified	<b>I mean litter size</b> (8.4 foetuses per female
in study report	compared to 95 in control)
in shudy report	malformations (bydranabrosis one
Dosa lavalor	nimel ingressed indications of showing
$\frac{\text{Dose levels:}}{0.5 \cdot 17.5 \cdot 20}$	animal, increased incidence of abiomatic
0, 5, 17.5, 50 mg/kg	terminal caudal vertebrae, mean % loetus:
bw/day	5.6% compared to 2.3% in control)
Vehicle: 1% aqueous	<u>30 mg/kg bw/day:</u>
methylcellulose	↑ <b>post-implantation loss</b> (%/No. of affected
	dams: 24.9/13 compared to 4.8/10 in control)
Gestation Days 7-28	<b>↑early intrauterine deaths</b> (1.0 compared to
	0.2 in control)
	<b>†late intrauterine deaths</b> (1.4 compared to
	0.3 in control)
	<b>mean litter size</b> (7.8 foetuses per female
	compared to 9.5 in control)
	litter weight (24%)
	snecific foetal variations (kidney
	cavitation additional liver lobe cervical
	remnant of thymus lengthened anterior
	fontanelle incomplete ossification of frontal
	and maxilla bones slight fusion of
	and maxima boiles, signification of
	scenieorae, asymmetric ossintation of
	cervical veneoral central
	- manormations (nyuronepnrosis, 2 animais;
	increased incidence of abnormal terminal
	caudal vertebrae, mean % toetus: 6.4%
	compared to 2.3% in control; misshapen
	nasal bone (8.0%, not present in historial ctr
	data at time for study); misaligned thoracic
	vertebral arch, one foetus, increased

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	incidence of absent frontal, mean % foetus:	
	8.9% compared to 0.0% in control)	

Study	NOAEL in study	Effect on non-	Other effects at the dose level of	Comments by study author	Comments by RMS
		reproductive endocrine	effect on non-reproductive		
		organ	endocrine organs		
Adrenals					
Long-term toxicity and	NOAEL for systemic toxicity was	<u>676 ppm:</u>	<u>52 ppm:</u>	The increase in adjusted organ	Increased adrenal
carcinogenicity	4 ppm (corresponding to 0.21 and	Adrenal:	-changes in urinalysis	weights in high dose females	weight was noted in
	0.28 mg/kg bw/day for males and	-increased rel weight in	(yellow/brown or orange	after 26 weeks of treatment was	females at a dose level
(RAR Vol. 3,	females, respectively) based on	females (week 27: 38%,	discoloration) (M, F)	explained in the study report to	with general toxicity
B.6.5.1/01)	reduced bodyweight gain noted in	week 104: 9%)	-changes in organ weights (Week	be fortuitous or related to the	(reduced bw gain: 28%)
	females at 676 ppm (38.3 mg/kg	-increased incidence of	27: ↑kidney (M: 8%))	slight growth retardation	and might be due to
Oral (dietary)	bw/day), changes in	benign	-histopathological changes in	observed in the high dose group	systemic toxicity
	haematological parameters noted	phaeochromocytoma	urinary bladder (epithelial		
No guideline claims	in both sexes at 676 ppm (37.6	-increased blood filled	hyperplasia (M, F), <u>kidneys</u>	While cystic degeneration	
presented in study	and 38.3 mg/kg bw/day in males	cyst in females (3	(epithelial hyperplasis (M, F), ↑	(blood filled cysts) is a common,	
report	and females, respectively),	compared to 1 in control	renal focal calcification (F), ureter	spontaneously arising non-	
	changes in biochemical	group)	(epithelial hyperplasia (M, F),	neoplastic lesion in the adrenal	
	parameters noted in both sexes at		<u>lungs</u> (arterial calcification (M))	cortex of females Sprague-	
Rat	676 ppm, changes in organ			Dawley rats, it can also be found	
Crl:CD(SD)BR	weights (increased kidney weight		<u>676 ppm:</u>	as a test article-related effect. It	
	noted in males at $\geq$ 52 ppm and in		-clinical signs (orange fur staining,	is a demanding challenge to	
50/sex/group	females at 676 ppm; increased		↓incidence of mass bearing	distinguish between	
	thyroid, thymus, heart and		animals) (M, F)	spontaneously occurred cystic	
GLP: No	adrenals noted in females at 676		↓ <b>bw gain</b> (toxicology evaluation:	degeneration and treatment-	
	ppm), changes in urinalysis noted		F: 28%; carcinogenicity	related damage. The incidence	
Dose levels:	in both sexes at ≥52 ppm (At 52		evaluation: F: 27%)	in blood filled cysts decreased	
Carcinogenicity	ppm and 676 ppm: yellow/brown		$\downarrow$ FC (M, F)	after 78 and 104 weeks of study	
groups:	to orange discoloration; At 676		-changes in haematological	duration. Since there were no	
0, 4, 52, 676 ppm	ppm: diuretic males),		<b>parameters</b> (\packed blood cell	further clear histopathological	
corresponding to	macroscopic changes noted in		volume (M week 27, 79; F week	indications of HPA axis	
0, 0.21, 2.82, 37.6	both sexes at 676 ppm		53), ↓haemoglobin (M: 8% week	disruption or disturbance (e.g.	
mg/kg bw/day in males	(discoloration in urinary bladder		27, F 5% week 27, 9% week 53),	atrophy or hypertrophy) an	
and 0, 0.28, 3.65, 49.4	and skin) and histopathological		$\downarrow$ red blood cell count (M week 27,	endocrine mechanism should	
mg/kg bw/day in	changes noted in both sexes at		79; F: week 27, 53))	not be assumed.	
temales	≥52 ppm.		-changes in biochemical		
			<b>parameters</b> (↑blood urea nitrogen		

### Table 2.6.8.3-03: Effects on non-reproductive organs

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·			
Chronic toxicology	NOAEL for tumour incidence	(M n.s., F n.s.), \calcium (M:	
groups:	was 52 ppm (corresponding to	week 27, 79; F: n.s.), ↓inorganic	
0, 4, 52, 676 ppm	2.82 and 3.65 mg/kg bw/day in	phosphorous (M: n.s, F: week 27,	
corresponding to 0,	males and females, respectively)	53), ↓lactate dehydrogenase (M:	
0.21, 2.89, 38.3 mg/kg	based on benign transitional cell	week 79, 103; F: week 103))	
bw/day in males; 0,	papillomas in urinary bladder and	-changes in organ weights (Week	
0.28, 3.72, 51.5 mg/kg	increased incidence of benign	27: †rel kidney (M: 15%),	
bw/day in females	phaeochromocytoma in adrenals	↑adrenals (F: 38%), Week 53:	
-	noted in both sexes at 676 ppm	1kidney (M: 10%), Week 79:	
Study was checked for		1 theart (M: 18%, F: 28%), 1 train	
compliance with		(F: 28%), ↑spleen (F. 13%),	
OECD TG 453 and		1kidney (F: 19%), Week 104:	
following deviations		↑brain (F: 23%), ↑thyroid	
were noted:		$(F:43\%)$ , $\uparrow$ (heart (F: 16%),	
i.Haematological		↑adrenals (F: 9%), ↑thymus (F:	
examination was not		50%))	
carried out at 3 months		-changes in urinalysis	
(the guideline		(vellow/brown or orange	
recommends		discoloration (M. F), diuretic	
measurements at 3		animals (M))	
months if effect was		-macroscopical changes in	
seen on		urinary bladder (orange	
haematological		discoloration of the urinary	
parameters in a		bladder serosa) (M. F) and skin	
previous 90 day study)		(orange staining (M, F))	
<i>ii. Prothrombin time</i>		-histopathological changes in	
and activated partial		urinary bladder (benign	
thromboplastin time		transitional cell papilloma (M. F).	
was not investigated		epithelial hyperplasia (M, F) polyp	
iii. Urea was not		(one female), chronic	
investigated		inflammation (M, F), kidneys	
iv. Uterus and		(epithelial hyperplasia (M, F).	
epididymides were not		renal papillary	
weighed		degeneration/necrosis (M_F) ↑	
v Coagulating gland		renal cortical scarring (M F)	
ileum lacrimal gland		pelvis polyp (one male). ↑ renal	
and seminal vesicle		focal calcification, ureter	
were not investigated		(epithelial hyperplasia (M, F).	
for historiathology		urethra (enithelial hyperplasia (M	
<i>joi msiopunoiogy</i>		F)), adrenals (benign	
		nhaeochromocytoma M F)	
		F)), <u>adrenals (benign</u> phaeochromocytoma M, F),	

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			pancreas ( pancreatic acinar		
			atrophy (M, F), <u>parathyroid</u>		
			(epithelial hyperplasia (M),		
			<u>mammary gland</u> (↓mammary		
			acinar development and secretion		
			(F)), <u>lungs</u> (arterial calcification		
			(M, F), <u>ovaries</u> (lack of cyclic		
			activity))		
Oral (dietary) 2-year	NOAEL for both sexes was set at	<u>250 ppm</u>	<u>250 ppm:</u>	According to the study authors	Increased incidence of
	10 ppm (0.33 and 0.31 mg/kg	<u>Adrenals</u>	-clinical signs (brown-tined urine)	increased cortical vacuolation	vacuolation of cortical
(RAR Vol 3,	bw/day in males and females,	-increased incidence of	↓bw (week 104: M: 8%, F: 6%)	must be seen as treatment	cells and increased
B.6.3.3.1/01)	respectively) based on mortalities	vacuolation of cortical	↓ <b>bw gain or bw loss</b> (week 0-52:	related adrenal lesion.	adrenal weights were
	noted in both sexes at 1000 ppm,	cells was noted in males	M: 1.9% compared to 2.4% in	Presumably the bad health	noted in males at dose
In house method	reduced bodyweight gain noted in	(3 animals compared to 0	controls, F: 2% compared to 1.7%	condition of the affected animals	levels with general
	both sexes at ≥250 ppm, changes	in control group)	in controls,	can be seen as the cause of	toxicity (body weight
Dog	in haematological parameters		week 52-104: M: -0.1% compared	cortical vacuolation (the dogs of	loss and
Beagle	(indicating anaemia) noted in		to 1.2% in controls,	the highest dose groups showed	histopathological
	both sexes at $\geq$ 50 ppm, changes in		F: 0.1% compared to 1.5% in	not only significant reduced	alterations in several
M, F	biochemical parameters	<u>1000 ppm</u>	controls)	body weight gain but even body	organs)
4/sex/dose	(indicating hepatotoxicity) noted	<u>Adrenals</u>	-changes in haematological	weight loss after 2-years of	
	in both sexes at ≥250 ppm,	-increased absolute and	parameters (\haemoglobin (M:	treatment. The animals appeared	
GLP: Yes	statistically significant changes in	relative weights were	week 26: 16%, week 52: 17%,	unhealthy with several further	
	relative organ weights (lung,	noted in males, while	week 76: 12%; F: week 26: 16%,	signs of general toxicity	
	spleen and gonads) noted in	decreased absolute	week 76: 20%), ↓haematocrit (M:	(anaemia, hepatotoxicity) and	
Dose levels:	females at 1000 ppm, changes in	weight was noted in	Weeks 26, 52, 76;	several histomorphological	
0, 2, 10, 50, 250 and	gross pathology noted at 50 ppm	females	F: Weeks 26, 76, 104),	alterations (lung, liver, kidney,	
1000 ppm (equivalent	(urinary bladder, spleen, ovary)	-increased vacuolation of	↓erythrocytes (M: Weeks 26, 52,	gonads).	
to 0, 0.06, 0.33, 1.42,	and 250 ppm (urinary bladder,	cortical cells was noted	76, 104; F: Weeks 76, 104):		
7.62 and 26.6 mg/kg	spleen, liver, ovary, kidneys) and	in males (3 animals	-changes in biochemistry:		
bw/day in males, and	1000 ppm (urinary bladder,	compared to 0 in control	(†serum glutamic-pyruvic		
0, 0.06, 0.31, 1.39,	spleen, ovary, liver, gall bladder,	group) and in females (3	transaminase (M, F), ↑alkaline		
6.79 and 29.1 mg/kg	kidneys, testes, ovary, heart, lung,	animals compared to 0 in	phosphatase (M, F),↑serum		
bw/day in females)	mesenteric lymph nodes) and	control group)	glutamic-oxaloacetic transaminase		
	histopathological changes noted		(M, F))		
	in the liver (in females at $\geq 50$		-macroscopical changes in		
	ppm; in males at ≥250 ppm),		urinary bladder (mucosal surface		
	urinary bladder (in both sexes at		brown or yellow-gray) <u>, liver</u>		
	$\geq$ 50 ppm), adrenals (in both sexes		(brown in colour, rough surfaced,		
	at $\geq$ 250 ppm), lungs (in both		tough in consistency, firm), spleen		
	sexes at ≥250 ppm), spleen (in		(dark in colour or margins dark),		

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males at 1000 ppm; in females at $\geq$ 250 ppm), kidneys (in both sexes at 1000 ppm, mesenteric lymph node (in females at 1000 ppm), gall bladder (in both sexes at 1000 ppm), pancreas (in females at 1000 ppm), aorta (one female at 1000 ppm), testis (1000 ppm) and ovaries (1000 ppm)	kidneys (depressed areas on surface), ovary (cyst on one), <u>lung</u> (white foci on surface) -histopathological changes in <u>adrenal</u> (↑vacuolation of cortical cells (M,F), focal nonsupparative adrenalitis (one male)), <u>lung</u> (foci of foamy macrophages (M,F)), <u>spleen</u> (extramedullary haematopoesis (F), congestion (F)), <u>liver</u> (pigment in cytoplasm of hepatocytes and kuppfer cells (M,F), pigment in macrophages (F), periportal fibrosis (M,F), bile	
	duct proliferation (M,F), bile plugs in canaliculi (one female), sinusoidal distension (F)), <u>kidney</u> (tubular nephrosis (one female), <u>urinary bladder</u> (pigment in mucosal cells (M,F), pigment laden macrophages (F))	
	1000 ppm: -mortality (one of each sex sacrificed in extremis during week 65) -clinical signs (brown-tined urine, orange stained hair around urogenital area, during the second year of study: pale appearing oral mucosal membranes, yellowish discoloration of the eyes and thinness in the female sacrificed in outcomic, and urbackbu	
	extremis, and unhealthy appearance characterized by thinness and lethargy in the male sacrificed in extremis) ↓ <b>bw</b> (week 52: M: 21%, F:26%; week 104: M: 23%, F: 33%)	

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	↓ <b>bw gain or bw loss</b> (Weeks 0-52:	
	M: 0.3% compared to 2.4% in	
	controls. F:	
	-0.6% compared to 1.7% in	
	controls: Weeks 52-104: M: 0.1%	
	compared to 1.2% in controls. F: -	
	0.6% compared to $1.5%$ in	
	controls)	
	-changes in haematological	
	<b>parameters</b> (all post treatment	
	intervals: haemoglobin M: up to	
	26%. F: up to 47%  haematocrit	
	(M, F).  erythrocytes $(M, F)$ :	
	$\uparrow$ platelet counts (F: Week 104)	
	-changes in biochemistry:	
	(†serum glutamic-pyruvic	
	transaminase (M, F), <sup>†</sup> alkaline	
	phosphatase (M, F), †bilirubin (F:	
	Weeks 52, 78). $\uparrow$ serum	
	glutamineo-oxaloacetic	
	transaminase (M, F))	
	-changes in organ weights: F: 1rel	
	lungs (92%) (F), $\uparrow$ rel spleen	
	$(77\%)$ (F). $\uparrow$ rel gonads (80%) (F).	
	↓rel gonads (55%) M, n.s), ↓rel	
	prostate (45%), n.s))	
	-macroscopical changes in the	
	liver (enlarged, lobes thickened	
	and pale, rough surface and	
	mottled, brown in colour, tough in	
	consistency, firm), gall bladder	
	(distended, walls thickened),	
	kidneys (small, depressed areas on	
	surface, contracted, polycystic-	
	primarily in the medulla, cortex	
	collapsed, thickened and opaque	
	areas on capsule), urinary bladder	
	(brown mucosa or tan in colour,	
	wall thickened, omentum adhered	
	to serosal surface), spleen (dark in	
	colour or margins dark, enlarged),	

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testes (small and soft), prostate
(small at week 52), <u>ovary</u> (cyst on
one), <u>heart</u> (reddish-brown
discoloration at coronary grove,
right A/V valve thickened and
vascular with dark raised area near
point of attachment at week 52),
lung (raised yellow gray foci on all
lobes, focal emphysematous
appearing areas), <u>cartilage</u> (yellow
to brown in colour), <u>trachea</u>
(brown or gray discoloration), <u>ribs</u>
(brown of gray discoloration),
tendons (brown or gray
discoloration), <u>bones</u> (gray in
colour), <u>mesenteric lymph nodes</u>
(dark in colour), <u>small intestine</u>
(walls slightly thickened)
-histopathological changes in
adrenal (†vacuolation of cortical
cells (M,F), necrosis, one female),
lung (foci of foamy macrophages
(M,F), focal pneumonitis (M, F),
cholesterol clefts (M,F), fibrosis
(one female), edema (M,F),
consolidation (one male)), <u>spleen</u>
(extramedullary haematopoesis
and congestion (M,F)), <u>liver</u>
(pigment in cytoplasm of
hepatocytes, kuppfer cells and
macrophages (M,F), periportal
fibrosis (M,F), bile duct
proliferation (M,F), bile plugs in
canaliculi (M,F), sinusoidal
distension (F)), <u>kidney</u> (tubular
nephropathy with fibrosis and
renal tubular regeneration (M,F)),
urinary bladder (pigment in
mucosal cells (M,F), edema (one
female), pigment laden
macrophages (one female)), testis

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			(aspermatogenesis, testicular atrophy, focal nonsuppurative orchitis), <u>ovary</u> (lack of follicle development, follicular cysts (one female), <u>mesenteric lymph nodes</u> (edema, erythrophagocytosis, distension of medullary sinuses (F)), <u>pancreas</u> (edema (F)), <u>gall</u> <u>bladder</u> (hyperplasia (M,F), papillary infolding (M,F), cholelith (one female)), <u>aorta</u> (mineralisation in one female), <u>small intestine</u> (focal enteritis (one female), erosion (one female))		
Carcinogenicity study	NOAEL was 3 ppm (0.38 and	30 ppm:	30 ppm:	Brown atrophy found in	No conclusive pattern.
	0.44 mg/kg bw/day for males and	Adrenals.	<b>↑mortality</b> (M, F)	females, might be induced by	•
(RAR Vol. 3	females, respectively) based on	-spindle cell hyperplasia	-clinical signs (orange fur staining)	exogenous steroid hormone	Brown athrophy was
B.6.5.2/01)	increased mortality noted in both	in females (32 animals	(M, F)	influence: however, it is also a	noted in females at 30
	sexes at $\geq 30$ ppm, reduced	compared to 29 in	-changes in organ weights (frel	common finding in aged	ppm and 300 ppm. The
Oral (dietary)	bodyweight gain $(33\%$ in males,	control group)	kidney, M: 14% n.s.)	rodents. Atrophic cortical tissue	dose response was not
No avidalina alaima in	$30\%$ in females) noted at $\geq 300$	-brown athrophy in	-histopathological changes in	was only found in females,	smooth.
No guidenne claims in	ppm, increased relative liver	lemales(15 animals	<u>adrenal</u> (adrenal spindle cell	which is contrary to males	The insidence of spindle
study report	ppm_increased relative kidney	group)	(E)); stomach (hyperkeratosis and	dominating the cortical	cell hyperplasia was
	weights noted in males at >30	group)	chronic inflammation (F))	histopathology	increased in females at
Mouse	ppm and in females at 300 ppm	300 ppm:		linstopathology	30 ppm but not at 300
Crl:CD-1 (ICR)BR	and histopathological changes	Adrenals:	300 ppm:	Cortical hyperplasia was found	ppm, and in males at
	noted in the adrenal and stomach	-spindle cell hyperplasia	↑mortality (M, F)	in males. This might be induced	300 ppm. However, the
50/sex/group	at $\geq$ 30 ppm and in the kidney,	in males 13 animals	-clinical signs (orange fur staining)	by xenobiotic action, e.g. steroid	incidences were low.
0	urether, urinary bladder, liver,	compared to 9 in control	(M, F)	hormone antagonists. However,	Also the increased
GLP: Yes	sciatic nerve, spleen, heart and	group)	↓ <b>bw gain</b> (M: 33%, F: 30%)	the incidence is very low (3	incidence of cortical
	lymph nodes noted at 300 ppm,	-cortical hyperplasia (3	-changes in organ weights (frel	animals out of 24) and taken	hyperplasia noted in
Dose levels:	and increased incidence of	animals compared to 1 in	liver (F: 20%), ↑rel kidney (M:	together with the histology	males at 300 ppm was
0, 3, 30 or 300 ppm	malignant lymphoma noted in	control group)	15% n.s., F: 24% n.s.), ↑rel heart	findings in females (atrophy) no	low.
(corresponding to	females at 300 ppm.	-brown athrophy in	(F), ↑brain (F))	consistent correlation is	
averages of 0, 0.38,		temales (8 animals	-histopathological changes in	recognizable.	
3.82 and $40.2$ mg/kg		compared to 2 in control	adrenai (Tadrenai spindle cell		
DW/day in males and $U$ ,		group)	(F) kidney (cortical coerring (M		
0.44, 4.48 and 40.4			$(\Gamma_{J})$ , Kidney (cortical scarring (M,		
			r), nyuronephrosis (NI, F)), <u>liver</u>		

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mg/kg bw/day in			(chronic inflammation (F), brown		
females)			pigmentation (F)), sciatic nerve		
			(degeneration (F)), spleen		
The study was checked			(haemosiderosis (F), <u>heart</u>		
for compliance with			(generalised periarteritis (F),		
OECD TG 451			myocardial fibrosis (13 M, 2 F)),		
(adopted 7 September			stomach (hyperkeratosis (M, F),		
2009). Following			epithelial hyperplasia (M), dilation		
deviations were noted:			of mucosal glands (M, F)), <u>urinary</u>		
i. the duration of study			<u>bladder</u> (epithelial hyperplasia		
was 20 months			(particularly F)), <u>urether</u> (dilation		
(according to the			(M, F)), <u>lymph nodes</u>		
guideline the duration			(histiocytosis (M, F), <u>lympho</u>		
of the study will			reticular tissue (malignant		
normally be 24 months			lymphoma (F))		
for rodents. Shorter or					
longer study durations					
may be used but should					
be justified).					
ii. cervix, coagulating					
gland, Hardian gland					
and lacrimal gland					
were not included in					
the histopathological					
evaluation.					
Thyroidea					
Oral (capsules) 90-day	NOAEL for both sexes was set at	<u>10 mg/kg bw/day:</u>	<u>3 mg/kg bw/day:</u>	As given in the study report the	Increased adjusted
study	3 mg/kg bw/day based on reduced	Thyroidea:	-clinical signs (coloured urine and	increase in the	thyroidea weight was
(Vol. 3,	bodyweight gain noted in females	-increased adjusted	faeces) (M, F)	thyroid/parathyroid weight is of	noted in males. The
B.6.3.2.2/01)	at $\geq 10 \text{ mg/kg bw/day and in}$	weight in males (33%)		uncertain etiology and the	effect could not be
	males at 30 mg/kg bw/day,		<u>10 mg/kg bw/dag:</u>	microscopic findings were not	explained and might be
OECD 409 (1998)	changes in haematological	<u>30 mg/kg bw/day:</u>	-clinical signs (coloured urine and	treatment related	indicative of endogenic
	parameters (indicating haemolytic	-increased adjusted	faeces) (M, F)		activity.
Dog	anaemia) noted in both sexes at	weight in males (32%)	↓bw gain (F: 12% n.s.)		
Beagle	≥10 mg/kg bw/day, changes in		$\downarrow$ FC (M)		
	biochemical parameters		-changes in haematological		
M, F	(indicating liver toxicity) noted in		parameters (\red blood cell count		
4/sex/dose	both sexes at 30 mg/kg bw/day,		(M, F), ↑reticulocyte count (M, F),		
	increased liver weight (noted in		↓mean cell haemoglobin		
GLP: Yes	females at $\geq 10$ mg/kg bw/day and				

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	in males at 30 mg/kg bw/day),	concentration (M, F), ↑platelet
Dose levels:	increased thyroid/parathyroid	count (F, n.s.), †platelet crit
0, 3, 10 and 30 mg/kg	weight noted in males at $\geq 10$	$(F, n.s.), \uparrow total white blood cell$
bw/day	mg/kg bw/day, increased spleen	count (F, n.s.))
-	weight noted in females at 30	-changes in organ weights
	mg/kg bw/day), gross pathology	(†adjusted liver (F: 27%),
	changes noted in females at 30	↑adjusted thyroid/parathyroid
	mg/kg bw/day (enlarged spleen.	(M: 33%))
	mottled liver and red bladder) and	-histopathological changes in
	histopathological changes noted	bone marrow (haemopoiesis (M.
	in the bone marrow (both sexes at	$\overline{F}$ ), liver (sinusoidal cell pigment
	>10 mg/kg bw/day), liver (both	characterised by presence of
	sexes at $\geq 10 \text{ mg/kg bw/dav}$ .	intracytoplasmic iron-containing
	urinary bladder (noted in females	njement (M, F)), urinary bladder
	at $\geq 10 \text{ mg/kg bw/dav and in}$	(cystitis (one female))
	males at 30 mg/kg bw/day).	
	kidney (noted in both sexes at 30	30  mg/kg bw/day
	mg/kg bw/day) and spleen (noted	-clinical signs (coloured urine and
	in both sexes at 30 mg/kg	faces) (M E)
	bw/day)	1  bw sain (M: 31%, F: 35%)
		IFC (M, F)
		-changes in haematological
		parameters () red blood cell count
		(M. F).  haemoglobin (M: 18%.
		F: 19%), packed cell volume (M.
		F), treficulocyte count (M, F).
		I mean cell haemoglobin
		concentration (M. F), tmean cell
		volume (M. F). <i>tplatelet count (M.</i>
		F), †platelet crit (M, F), †total
		white blood cell count (M, F))
		-changes in biochemistry (↑mean
		total bilirubin (M, F))
		-changes in organ weights
		(1 adjusted liver (M: 20%, F: 29%),
		↑adjusted thyroid/parathyroid (M:
		$32\%$ ), $\uparrow$ adjusted spleen (F: 56%)
		n.s.))
		-macroscopic changes in spleen
		(enlarged two females), liver

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					1
			(mootied, one female) and <u>urinary</u>		
			-histonathological changes in		
			bone marrow (haemopoiesis		
			characterised by greater cellularity		
			(M, F)), spleen (haemopoiesis		
			characterised by increased		
			haemopoietic cells in the red pulp		
			(M, F), congestion of the splenic		
			red pulp (M, F)), liver (sinusoidal		
			cell pigment characterised by		
			presence of intracytoplasmic iron-		
			containing pigment (M, F), bile		
			duct hyperplasia (M, F)), kidney		
			(pigment (M, F)), <u>urinary bladder</u>		
			(transitional cell hyperplasia (M,		
			F), arteritis (one male), cystitis		
			(one remaie))		
Long-term toxicity and	NOAEL for systemic toxicity was	676 ppm:	<u>52 ppm:</u>	All findings were according to	Adjusted thyroid weight
carcinogenicity	4 ppm (corresponding to 0.21 and	Thyroid:	-changes in urinalysis	the author spontaneous findings	was increased in
	0.28  mg/kg bw/day for males and	-increased adjusted	(yellow/brown or orange	in laboratory rats and show no	females of the high dose
(KAK V 0I. 3, D < 5 1/01)	remales, respectively) based on	weight in females at 104	discoloration) (M, F)	clear relationship to treatment	at week 104 (43%), but
B.0.5.1/01)	females at 676 mm (28.2 mm/s	weeks (43%)	-changes in organ weights (week $27$ , this is a set (M, 89())	After 104 mester in females	no histopathological
Oral (diatam)	hu/day) changes in		2/: [Kidney (W: 8%)]	Alter 104 weeks in lemales,	changes were noted
Ofal (uletaly)	balantological parameters noted		uringry bladder (epithelial	nom indicating no consistent	
No guideline claims	in both sexes at 676 ppm (37.6		hyperplasia (M F) kidneys	dose-dependent effect over time	
presented in study	and 38.3 mg/kg bw/day in males		(enithelial hyperplasis (M F) $\uparrow$	or as a function of time of	
report	and females respectively)		renal focal calcification (F), ureter	treatment	
report	changes in biochemical		(epithelial hyperplasia (M, F).	douthont	
	parameters noted in both sexes at		lungs (arterial calcification (M))		
Rat	676 ppm, changes in organ				
Crl:CD(SD)BR	weights (increased kidney weight		<u>676 ppm:</u>		
	noted in males at $\geq$ 52 ppm and in		-clinical signs (orange fur staining,		
50/sex/group	females at 676 ppm; increased		↓incidence of mass bearing		
	thyroid, thymus, heart and		animals) (M, F)		
GLP: No	adrenals noted in females at 676		↓bw gain (toxicology evaluation:		
	ppm), changes in urinalysis noted		F: 28%; carcinogenicity		
	in both sexes at $\geq$ 52 ppm (At 52		evaluation: F: 27%)		
	ppm and 676 ppm: yellow/brown		$\downarrow$ FC (M, F)		

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Dose levels:	to orange discoloration; At 676	-changes in haematological	
Carcinogenicity	ppm: diuretic males),	parameters (↓packed blood cell	
groups:	macroscopic changes noted in	volume (M week 27, 79; F week	
0, 4, 52, 676 ppm	both sexes at 676 ppm	53), thaemoglobin (M: 8% week	
corresponding to	(discoloration in urinary bladder	27, F 5% week 27, 9% week 53),	
0, 0.21, 2.82, 37.6	and skin) and histopathological	↓red blood cell count (M week 27,	
mg/kg bw/day in males	changes noted in both sexes at	79; F: week 27, 53))	
and 0, 0.28, 3.65, 49.4	≥52 ppm.	-changes in biochemical	
mg/kg bw/day in		parameters (†blood urea nitrogen	
females	NOAEL for tumour incidence	$(M n.s., F n.s.)$ , $\downarrow$ calcium $(M:$	
	was 52 ppm (corresponding to	week 27, 79; F: n.s.), <i>inorganic</i>	
Chronic toxicology	2.82 and 3.65 mg/kg bw/day in	phosphorous (M: n.s, F: week 27,	
groups:	males and females, respectively)	53). Llactate dehydrogenase (M:	
0, 4, 52, 676 ppm	based on benign transitional cell	week 79, 103; F: week 103))	
corresponding to 0,	papillomas in urinary bladder and	-changes in organ weights (Week	
0.21, 2.89, 38.3 mg/kg	increased incidence of benign	27: †rel kidney (M: 15%),	
bw/day in males; 0,	phaeochromocytoma in adrenals	$\uparrow$ adrenals (F: 38%),	
0.28, 3.72, 51.5 mg/kg	noted in both sexes at 676 ppm	Week 53: †kidney (M: 10%),	
bw/day in females		Week 79: 1 heart (M: 18%, F:	
5		28%), †brain (F: 28%), †spleen	
Study was checked for		(F. 13%), ↑kidney (F: 19%),	
compliance with		Week 104: 1brain (F: 23%).	
OECD TG 453 and		$\uparrow$ thyroid (F:43%), $\uparrow$ (heart (F:	
following deviations		16%), $\uparrow$ adrenals (F: 9%), $\uparrow$ thymus	
were noted:		(F: 50%))	
i.Haematological		-changes in urinalysis	
examination was not		(vellow/brown or orange	
carried out at 3 months		discoloration (M, F), diuretic	
(the guideline		animals (M))	
recommends		-macroscopical changes in urinary	
measurements at 3		bladder (orange discoloration of	
months if effect was		the urinary bladder serosa) (M, F)	
seen on		and skin (orange staining (M, F))	
haematological		-histopathological changes in	
parameters in a		urinary bladder (benign	
previous 90 day study)		transitional cell papilloma (M. F).	
ii. Prothrombin time		epithelial hyperplasia (M, F) polyp	
and activated partial		(one female), chronic	
thromboplastin time		inflammation (M, F), kidneys	
was not investigated		(epithelial hyperplasia (M, F),	
		renal papillary	

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iii. Urea was not	degeneration/necrosis (M, F) ↑
investigated	renal cortical scarring (M, F)
iv. Uterus and	pelvis polyp (one male), ↑ renal
epididymides were not	focal calcification, ureter
weighed	(epithelial hyperplasia (M, F),
v. Coagulating gland,	urethra (epithelial hyperplasia (M,
ileum, lacrimal gland	F)), <u>adrenals</u> (benign
and seminal vesicle	phaeochromocytoma M, F),
were not investigated	pancreas (↑pancreatic acinar
for histopathology	atrophy (M, F), <u>parathyroid</u>
	(epithelial hyperplasia (M),
	mammary gland (\mammary
	acinar development and secretion
	(F)), <u>lungs</u> (arterial calcification
	(M, F), <u>ovaries</u> (lack of cyclic
	activity))

### 2.6.9 Summary of medical data and information

### 2.5.9.1 Medical surveillance on manufacturing plant personnel and monitoring studies

No hazardous incident had occurred with workers in the production facilities of quinoclamine and its formulated products.

### 2.5.9.2 Data collected on human

No experiences from humans are available

### 2.5.9.3 Direct observations

No experiences from humans are available

### 2.5.9.4 Epidemiological studies

No experiences from humans are available

### 2.5.9.5 Diagnosis of poisoning (determination of active substance, metabolites), Specific signs of poisoning, clinical tests

No experiences from humans are available

### 2.5.9.6 Proposes treatment; first aid measures, antidotes, medical treatment

First-aid measures:

*Eyes:* Rinse with sufficient water if an irritating feeling is presented. Receive medical examination and treatment if necessary.

*Skin:* Take off contaminated clothing and wash the skin with soap and water. Receive medical examination and treatment if an irritating feeling is presented.

Inhalation: Move to a clean zone at once. Receive medical examination and treatment if necessary.

Ingestion: Get the person to vomit as soon as possible (decontamination). Receive medical examination and treatment.

*Medical treatment, antidotes:* Decontamination as soon as possible. Symptomatic treatment. No antidotes available

*Expected symptoms of poisoning:* Brown-tinged urine, anorexia and/or lethargy are expected. Systemic intoxication in human is not known.

### 2.6.10 Toxicological end points for risk assessment (reference values)

## 2.6.10.1 Toxicological end point for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake)

The ADI represents the maximum dose of a substance that can be ingested on a daily basis without bringing unacceptable risks to human health. Ideally, the ADI is derived from a NOAEL obtained in a long-term study.

The current EU Annex I endpoint for the ADI is 0.002 mg/kg bw/day (Review Report for quinoclamine SANCO/3622/07-rev 1, 1 January 2008) based on the NOAEL of 0.2 mg/kg bw obtained in the 2 year rat study, and a safety factor of 100.

No new value is proposed for the Annex I renewal of quinoclamine. The NOAEL of 0.2 mg/kg bw/day obtained in the 2-year rat study is considered an appropriate basis for the ADI of quinoclamine. Using an uncertainty factor of 100, the proposed ADI is 0.002 mg/kg bw/day. With respect to the dose levels where neoplastic changes were noted in the rat long-term toxicity study (37.6 mg/kg bw/day) and where teratogenic effects were observed in the rabbit developmental toxicity study (17.5 mg/kg bw/day) there is a margin of safety above 1000.

	NOAEL	Study	Safety factor
ADI: 0.002 mg/kg bw/day	0.2 mg/kg bw/day	Rat 2 year	100
		Anonymous 23 1991	
		Study Report: AKJ/7/90	

### 2.6.10.1.1 Drinking water limit

The maximum admissible concentration of an active substance is 0.1 µg/L (according to Directive 89/778/EEC).

A health-based limit (adult) of 0.012 mg/L ( $12 \mu g/L$ ) can be derived assuming 20% of the ADI, water consumption of 2 L/day and bodyweight of 60 kg. The calculation of this value is:

 $C_{max}$  water= (ADI x 20% x Bodyweight)/2L = (0.002x 0.2x 60 kg)/2L = 0.012 mg/L (12 µg/L). Since this value is higher than the maximum permissible groundwater concentration of 0.1 µg/L, the Cmax water calculated should not be used.

A health-based limit (infant) of 0.0027 mg/L ( $2.7 \mu g/L$ ) can be derived assuming 20% of the ADI, water consumption of 0.75 L/day and bodyweight of 5 kg. The calculation of this value is:

 $C_{max}$  water= (ADI x 20% x Bodyweight)/0.75L = (0.002 x 0.2x 5 kg)/0.75L = 0.0027 mg/L (2.7 µg/L). Since this value is higher than the maximum permissible groundwater concentration of 0.1 µg/L, the Cmax water calculated should not be used.

## 2.6.10.2 Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

The ARfD represents the maximum dose of a substance that can be ingested on a single occasion without bringing an unacceptable risk to human health. It is usually derived from a NOAEL based on an acute effect occurring after a single exposure in an oral study. According to the guidance document (Guidance for the setting of an acute reference dose (ARfD) 7199/VI/99 rev 6), the NOAEL obtained in the most sensitive species should be considered.

The current EU Annex I endpoint for the ARfD is 0.05 mg/kg bw/day (Review Report for quinoclamine SANCO/3622/07-rev 1, 1 January 2008) based on the 28-day rat study supported by the developmental rat study, with the use of a safety factor of 100.

No new value is proposed for the Annex I renewal of quinoclamine. The NOAEL of 5 mg/kg bw/day obtained in the 28-day rat study and the developmental toxicity studies in the rat and rabbit (NOAELs of 5 mg/kg bw/day), is considered an appropriate basis for the ARfD of quinoclamine. Using an uncertainty factor of 100, the proposed ARfD is 0.05 mg/kg bw. With respect to the dose levels where neoplastic changes were noted in the rat long-term toxicity study (37.6 mg/kg bw/day) there is a margin of safety of 752. With the respect to the dose levels where teratogenic effects were observed in the rabbit developmental toxicity study (17.5 mg/kg bw/day) there is a margin of safety of 350.

In the 28-day rat study changes indicating haematolytic anemia were noted at a dose level of 44 mg/kg bw/day.In the developmental studies in the rat and rabbit developmental effects were noted at the dose level of 20 mg/kg bw/day.

	NOAEL	Study	Safety
			factor
<b>ARfD:</b> 0.05	5 mg/kg	Rat 28-day	100
mg/kg bw	bw/day	Anonymous 15 (2002) Study Report: 619/148	
		Developmental rat and rabbit (maternal and developmental NOAELs of 5 mg/kg bw/day) Anonymous 25 (1986) Study Report: AKJ/4/86 Anonymous 26 (2002) Study Report: 619/94-D6154 Anonymous 29 (2002) Study Report: 619/155-D6154	

# 2.6.10.3 Toxicological end point for assessment of occupational, bystander and residents risks – AOEL (acceptable operator exposure level)

The current EU Annex I endpoint for the AOEL is 0.03 mg/kg bw (Review Report for quinoclamine SANCO/3622/07 – rev 1, 1 February 2008) based on NOAEL of 3 mg/kg bw/day obtained in the 90-day dog study, with the use of a safety factor of 100.

No new value is proposed for the Annex I renewal of quinoclamine. The NOAEL of 3 mg/kg bw/day obtained in the 90-day dog study, supported by the 90-day rat studies (NOAELs at 3 mg/kg bw/day) is considered an appropriate basis for the AOEL of quinoclamine. Using an uncertainty factor of 100 the proposed AOEL is 0.03 mg/kg bw/day. With respect to the lowest dose levels where teratogenic effects were observed in the rabbit study (17.5 mg/kg bw/day), there is a margin of safety of 583. Based on the teratogenic findings in rats and rabbits the classification of quinoclamine as toxic for reproduction in Category 2 is proposed. With respect to the lowest dose levels where neoplastic changes were observed in the rat long-term study (37.6 mg/kg bw/day), there is a margin of safety of 1253.

The critical effect of haemolytic anemia was considered as the most relevant endpoint for the setting of AOEL. Results of the 90-day dog study (B.6.3.2.2/01) showed changes indicating haemolytic anemia at the LOAEL of 10 mg/kg bw/day (pigment in the liver, characterised by presence of intracytoplasmic iron-containing pigment). In one 90-day oral rat study (B.6.3.2.1/01) changes indicating haemolytic anemia were noted at the LOAEL of 13 mg/kg bw/day (increased hemosiderin deposition in the spleen). In a second 90-day oral rat study (B.6.3.2.1/02) changes indicating haemolytic anaemia were noted at the LOAEL of 13.89 mg/kg bw/day (dark straw colored urine, increased relative spleen weight, histopathological changes of increased extent of pigment in the spleen and liver).

No NOAEL for females could be established in the second 90-day oral rat study, due to reduced bodyweight gain (>10%) noted in females at  $\geq$ 50 ppm ( $\geq$ 4.56 mg/kg bw/day). However, reduced bodyweight gain was not noted at the dose level of 3.72 mg/kg bw/day in the long-term toxicity study using the same strain of animals (CD-rat). Furthermore, no adverse effect on bodyweight gain was noted in the first 90-day oral rat study with Sprague-Dawley rats tested at doses up to 65 mg/kg bw/day. Thus, the effect on bodyweight noted in the second 90-day oral rat study was considered to be covered by the NOAEL of 3 mg/kg bw/day obtained in the 90-day dog study.

In the 2-year dog study, findings indicative of anaemia (pigment in liver) were noted at the dose level of 50 ppm (1.39/1.42 mg/kg bw/day in males and females, respectively). This study was, however not considered for the AOEL setting, since the exposure duration (1/6 of the lifespan for beagle dogs) was not considered as a typically short-term exposure.

	NOAEL	Study	Safety factor
AOEL: 0.03 mg/kg bw/day	3 mg/kg bw/day	90-day dog	100
		Anonymous 20 (2002) Study Report.: 0619/134	
		90-day rat (NOAEL of 3 mg/kg bw/day)	
		Anonymous 18 (2003) Study report: 0619/132	

## 2.6.10.4 Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL (acute acceptable operator exposure level)

The following value for AAOEL is proposed for the renewal of quinoclamine:

An AAOEL based on the 28-day rat study and the developmental rat studies, resulting in a value of 0.05 mg/kg bw (applying an uncertainty factor of 100).

In the 28-day rat study changes indicating haematolytic anemia were noted at a dose level of 44 mg/kg bw/day. In the developmental rat studies developmental effects were noted at the dose level of 20 mg/kg bw/day.

	NOAEL	Study	Safety factor
AAOEL: 0.05 mg/kg bw	5 mg/kg bw/day	Rat 28-day	100
		Anonymous 15 (2002) Study Report: 619/148	
		Developmental rat (maternal NOAELs of 5 mg/kg bw/day)	
		Anonymous 25 (1986) Study Report AKJ/4/86	
		Anonymous 26 (2002) Study Report: 619/94-D6154	

### 2.6.11 Summary of product exposure and risk assessment

Mogeton Top is a wettable granule (WG) containing 500 g/kg quinoclamine.

The critical GAP for the re-approval of quinoclamine is based on the use of the representative formulation Mogeton Top. Mogeton Top is intended to be used as a herbicide on golf greens and in nursery stock plants (potted).

Usage information pertinent to operator exposure is summarized in the Table 2.6.11-01.

Crop (field)	F/G Application rate		Spray dilution Number of	Application equipment		
		[L	[g	[L/ha]	applications	
		product/ha]	a.i./ha]			
Golf greens	F	7.5	3750	1000	1	Downward spraying
Golf greens	F	7.5	3750	1000	1	Hand-held spraying
Nursery stock	F	7.5	3750	1000	1	Hand-held spraying
plants (potted)						(pots on permeable sheets, no
						application on flowering plants)
Nursery stock	F	2.88	1440	800	1	Downward spraying
plants (potted)						(pots on permeable sheets, no
						application on flowering plants)
Nursery stock	G*	7.5	3750	1000	1	Hand-held spraying
plants (potted)						(pots on permeable sheets)
Nursery stock	G	1.62	810	450	1	Hand-held spraying
plants (potted)						(pots on permeable sheets)

 Table 2.6.11-1: Summary of use patterns for the active substance quinoclamine in Mogeton Top.

F: field use

G: greenhouse use

G\*: greenhouse use including walk-in tunnel

Dermal absorption data are available for quinoclamine from an in vitro study with human/rat skin (Rijk J.C.W., 2015, Report No. 506990) reported in Vol. 3 (Product), section B.6.2). Derived from the results of this study, dermal absorption rates of 0.9% (concentrate), 1% (spray dilution at 3.74 g/L) and 3% (spray dilution at 1.8 g/L) were proposed.

The results of the exposure calculations for operators, bystanders, residents and workers are summarized in Tables 2.6.11-2 to 7.

Model data	PPE	Total systemic exposure (mg/kg	% of AOEL <sup>1)</sup>
Colf groons application rate 375	a a i /ha vahiala mountad daw	DW/day)	
Gon greens, application rate 575	o g a.i./na, venicie mounteu uow	nwaru spraying, neiu	
50 ha/day	Potential exposure	0.0291	97.05
60 kg bw	+ work wear	0.0195	61.15
1.0 % dermal absorption (in-use)	(arms, body and legs covered)		
0.9 % dermal absorption (conc.)			
Golf greens, application rate 375	0 g a.i./ha, hand-held downward	spraying, field	
1 ha/day	Potential exposure	0.0437	145.55
60 kg bw	+ work wear	0.0101	33.52
1.0 % dermal absorption (in-use)	(arms, body and legs covered)		
0.9 % dermal absorption (conc.)			
Nursery stock plants (potted plan	nts)*, application rate 3750 g a.i.	/ha, hand-held downward	spraying, field
EFSA calculator	Potential exposure	0.0437	145.55
1 ha/day	+ work wear	0.0101	33.52
60 kg bodyweight	(arms, body and legs covered)		
1.0 % dermal absorption (in-use)			
0.9 % dermal absorption (conc.)			

### Table 2.6.11-02: Predicted systemic exposure of operator as a proportion of the AOEL using the EFSA calculator.

Nursery stock plants (potted plants)*, application rate 1440 g a.i./ha, hand-held downward spraying, field				
EFSA calculator	Potential exposure	0.0476	158.69	
1 ha/day	+ work wear	0.0075	25.03	
60 kg bodyweight	(arms, body and legs covered)			
3.0 % dermal absorption (in-use)				
0.9 % dermal absorption (conc.)				
Nursery stock plants (potted plan	nts)*, application rate 1440 g a.i.	/ha, vehicle mounted down	nward spraying, field	
EFSA calculator	Potential exposure	0.0322	107.46	
10 ha/day	+ work wear	0.0153	50.84	
60 kg bodyweight	(arms, body and legs covered)			
3.0 % dermal absorption (in-use)				
0.9 % dermal absorption (conc.)				

<sup>1)</sup> AOEL 0.03 mg/kg bw/day

Table 2.6.11-3. Predicted systemic exposure of operator as a proportion of the AOEL using the Dutch Greenhouse model.

Model data	PPE	Total systemic	% of AOEL <sup>1)</sup>
		exposure (mg/kg	
		bw/day)	
Nursery stock plants (potted plan	nts), application rate 3750 g a.i./h	na, downward spraying, h	and-held, greenhouse <sup>2)</sup>
Dutch greenhouse Model	Without PPE	0.1875	625
1 ha/day	With PPE	0.075	250
60 kg bodyweight	(coverall, gloves)		
1.0 % dermal absorption (in-use)	With PPE	0.01875	63
0.9 % dermal absorption (conc.)	(coverall, gloves and		
	respiratory protection)		
Nursery stock plants (potted plan	nts), application rate 810 g a.i./ha	a, downward spraying, ha	nd-held, greenhouse
Dutch greenhouse Model	Without PPE	0.0945	315
1 ha/day	With PPE	0.0216	72
60 kg bodyweight	(coverall, gloves)		
3.0 % dermal absorption (in-use)	With PPE	0.00945	32
0.9 % dermal absorption (conc.)	(coverall, gloves and		
	respiratory protection)		

1) AOEL 0.03 mg/kg bw/day

2) Including walk-in tunnels

Model data	Quinoclamine			
	Exposure pathway	Total absorbed dose [mg/kg bw/day]	% of systemic AAOEL <sup>1)</sup>	
Golf greens, application rate 3750 g a	a.i./ha, vehicle mounted downward spraying,	field		
EFSA calculator	Spray drift (95th percentile)	0.0007	1.30	
Drift rate: 8.5 % (2-3 m) Body weight (adult): 60 kg 1.0 % dermal absorption (in-use)	Vapour (95th percentile)	0.0002	0.46	
	Surface deposits (95th percentile)	0.0008	1.54	
0.9 % dermal absorption (conc.)	Entry into treated crops (95th percentile)	0.0011	2.27	
EFSA calculator	Spray drift (95th percentile)	0.0027	5.39	
Drift rate: 8.5 % (2-3 m) Body weight (child): 10 kg 1.0 % dermal absorption (in-use) 0.9 % dermal absorption (conc.)	Vapour (95th percentile)	0.0011	2.14	
	Surface deposits (95th percentile)	0.0096	19.25	
	Entry into treated crops (95th percentile)	0.0306	61.13	

 Table 2.6.14-4. Predicted systemic exposure to bystanders as a proportion of the AAOEL using the EFSA calculator.

Exposu Golf greens, application rate 3750 g a.i./ha, ha	re pathway nd-held downward spraying, field rift (95th percentile)	Total absorbed dose [mg/kg bw/day]	% of systemic AAOEL <sup>1)</sup>
Golf greens, application rate 3750 g a.i./ha, ha	nd-held downward spraying, field		
	rift (95th percentile)		
EFSA calculator Spray d	() + F)	0.0007	1.30
Drift rate: 8.5 % (2-3 m) Pody weight (adult): 60 kg	(95th percentile)	0.0002	0.46
1.0 % dermal absorption (in-use) Surface	deposits (95th percentile)	0.0008	1.54
0.9 % dermal absorption (conc.) Entry in	to treated crops (95th percentile)	0.0011	2.27
EFSA calculator Spray d	rift (95th percentile)	0.0027	5.39
Drift rate: 8.5 % (2-3 m) Body weight (child): 10 kg	(95th percentile)	0.0011	2.14
1.0 % dermal absorption (in-use) Surface	deposits (95th percentile)	0.0096	19.25
0.9 % dermal absorption (conc.) Entry in	to treated crops (95th percentile)	0.0306	61.13
Nursery stock plants, scenario ornamentals, a	pplication rate 3750 g a.i./ha, hand-	held downward spray	ing, field
EFSA calculator Spray d	rift (95th percentile)	0.0007	1.30
Drift rate: 8.5 % (2-3 m) Pody weight (adult): 60 kg	(95th percentile)	0.0002	0.46
1.0 % dermal absorption (in-use) Surface	deposits (95th percentile)	0.0008	1.54
0.9 % dermal absorption (conc.) Entry in	to treated crops (95th percentile)	0.0035	7.03
EFSA calculator Spray d	rift (95th percentile)	0.0027	5.39
Drift rate: 8.5 % (2-3 m) Body weight (child): 10 kg	(95th percentile)	0.0011	2.14
1.0 % dermal absorption (in-use) Surface	deposits (95th percentile)	0.0096	19.25
0.9 % dermal absorption (conc.) Entry in	to treated crops (95th percentile)	0.0063	12.66
Nursery stock plants, scenario ornamentals, a spraying, field	pplication rate 1440 g a.i./ha, vehicl	le mounted and hand-h	eld downward
EFSA calculator Spray d	rift (95th percentile)	0.0009	1.82
Drift rate: 8.5 % (2-3 m) Pody weight (adult): 60 kg	(95th percentile)	0.0002	0.46
3.0 % dermal absorption (in-use) Surface	deposits (95th percentile)	0.0009	1.77
0.9 % dermal absorption (conc.) Entry in	to treated crops (95th percentile)	0.0041	8.10
EFSA calculator Spray d	rift (95th percentile)	0.0035	6.96
Drift rate: 8.5 % (2-3 m) Body weight (child): 10 kg	(95th percentile)	0.0011	2.14
3.0 % dermal absorption (in-use) Surface	deposits (95th percentile)	0.0050	9.94
0.9 % dermal absorption (conc.) Entry in	to treated crops (95th percentile)	0.0073	14.58

<sup>1)</sup> AAOEL 0.05 mg/kg bw/day

Model data	Quinoclamine						
	Exposure pathway	Total absorbed dose [mg/kg bw/day]	% of systemic AOEL <sup>1)</sup>				
Golf greens, application rate 3750	g a.i./ha, vehicle mounted and hand-held do	wnward spraying, f	field				
EFSA calculator	Spray drift (75th percentile)	0.002	0.82				
Drift rate: 5.6 % (2-3 m) Body weight (adult): 60 kg	Vapour (75th percentile)	0.002	0.77				
1.0 % dermal absorption (in-use) 0.9 % dermal absorption (conc.)	Surface deposits (75th percentile)	0.003	0.85				
	Entry into treated crops (75th percentile)	0.006	1.90 <sup>2)</sup>				
	All pathways (mean)	0.011	3.69				

 Table 2.6.14-5: Predicted systemic exposure to residents as a proportion of the AOEL using the EFSA calculator.

Model data	Quinoclamine						
	Exposure pathway	Total absorbed dose [mg/kg bw/day]	% of systemic AOEL <sup>1)</sup>				
EFSA calculator	Spray drift (75th percentile)	0.0011	3.63				
Drift rate: 5.6 % (2-3 m) Body weight (child): 10 kg	Vapour (75th percentile)	0.0011	3.57				
1.0 % dermal absorption (in-use)	Surface deposits (75th percentile)	0.0036	11.97				
0.9 % dermal absorption (conc.)	Entry into treated crops (75th percentile)	0.0244	81.41 <sup>2)</sup>				
	All pathways (mean)	0.0055	18.45				
Nursery stock plants, scenario ornan	nentals, application rate 3750 g a.i./ha, ha	nd-held downward	spraying, field				
EFSA calculator	Spray drift (75th percentile)	0.0002	0.82				
Drift rate: 5.6 % (2-3 m) Body weight (adult): 60 kg	Vapour (75th percentile)	0.0002	0.77				
1.0 % dermal absorption (in-use)	Surface deposits (75th percentile)	0.0003	0.85				
0.9 % dermal absorption (conc.)	Entry into treated crops (75th percentile)	0.0035	11.72				
	All pathways (mean)	0.0033	11.13				
EFSA calculator	Spray drift (75th percentile)	0.0011	3.63				
Drift rate: 5.6 % (2-3 m) Body weight (child): 10 kg	Vapour (75th percentile)	0.0011	3.57				
1.0 % dermal absorption (in-use)	Surface deposits (75th percentile)	0.0036	11.97				
0.9 % dermal absorption (conc.)	Entry into treated crops (75th percentile)	0.0063	21.09				
	All pathways (mean)	0.0094	31.21				
Nursery stock plants, scenario ornan spraying, field	nentals, application rate 1440 g a.i./ha, vel	nicle mounted and h	and-held downward				
EFSA calculator	Spray drift (75th percentile)	0.0003	1.17				
Drift rate: 5.6 % (2-3 m) Body weight (adult): 60 kg	Vapour (75th percentile)	0.0002	0.77				
3.0 % dermal absorption (in-use)	Surface deposits (75th percentile)	0.0003	0.98				
0.9 % dermal absorption (conc.)	Entry into treated crops (75th percentile)	0.0041	13.50				
	All pathways (mean)	0.0038	12.81				
EFSA calculator	Spray drift (75th percentile)	0.0015	4.96				
Drift rate: 5.6 % (2-3 m) Body weight (child): 10 kg	Vapour (75th percentile)	0.0011	3.57				
3.0 % dermal absorption (in-use)	Surface deposits (75th percentile)	0.0018	5.99				
0.9 % dermal absorption (conc.)	Entry into treated crops (75th percentile)	0.0073	24.30				
	All pathways (mean)	0.0090	30.09				

<sup>1)</sup> AOEL 0.03 mg/kg bw/day
 <sup>2)</sup> Scenario not relevant, covered by recreational exposure scenario

Model data	Quinoclamine					
	Total absorbed dose [mg/kg bw/day] % of systemic AOEL <sup>1)</sup>					
Golf greens, application rate 3750 g a.i./ha, vehicle mounted and hand-held downward spraying, field						
EFSA calculator	0.0046	15.21				
Exposure: 2 hours						
Body weight (adult): 60 kg						
1.0 % dermal absorption (in-use)						
0.9 % dermal absorption (conc.)						
EFSA calculator	0.064	213.75				
Exposure: 2 hours						
Body weight (child): 10 kg						
1.0 % dermal absorption (in-use)						
0.9 % dermal absorption (conc.)						

Table 2.6.14-6. Predicted systemic recreational exposure as a proportion of the AOEL using the EFSA calculator.

Model data	Quinoclamine	Quinoclamine						
	Total absorbed dose [	Total absorbed dose [mg/kg bw/day] % of systemic AOEL <sup>1)</sup>						
Refined recreational exposure considering dermal exposure only for the child								
Golf greens, application rate 3750 g a.i./ha, vehicle mounted and hand-held downward spraying, field								
EFSA calculator	0.00975	32.50						
Exposure: 2 hours								
Body weight (child): 10 kg								
1.0 % dermal absorption (in-use)								
0.9 % dermal absorption (conc.)								

<sup>1)</sup> AOEL 0.03 mg/kg bw/day

### Model data Level of personal Operator exposure % of AOEL<sup>1</sup>

Niodel data	Level of personal	Operator exposure	% OI AUEL
	protective equipment	[mg/kg bw/day]	
Golf greens, application rate 3750 g a	a.i./ha, vehicle mounted and han	d-held downward spraying	g, field
EFSA calculator	Potential exposure	0.0870	290.00
8 hours/day			
60 kg bodyweight	+ work wear	0.0375	125.00
TC:	(arms body and legs covered)	0.0375	123.00
5800 cm <sup>2</sup> /hour (potential exp.)		0.0007	20.00
2500 cm <sup>2</sup> /hour (work wear)	+ work wear and gloves	0.0087	29.00
580 cm <sup>2</sup> /hour (work wear+gloves)			
1.0 % dermal absorption (in-use)			
0.9 % dermal absorption (conc.)			
Golf greens, application rate 1875 g a	a.i./ha, downward spraying, vehi	cle mounted, field	
EFSA calculator	Potential exposure	0.0435	145.00
8 hours/day	-		
60 kg bodyweight	+ work wear	0.0188	62.50
TC:	(arms, body and legs covered)	0.0100	02.00
5800 cm <sup>2</sup> /hour (potential exp.)	L work wear and gloves		14 50
2500 cm <sup>2</sup> /hour (work wear)	+ WOIK wear and gloves	0.0044	14.30
580 cm <sup>2</sup> /hour (work wear+gloves)			
1.0 % dermal absorption (in-use)			
0.9 % dermal absorption (conc.)			
Nursery stock plants (potted plants)*	<sup><i>k</i></sup> , application rate 3750 g a.i./ha,	downward spraying, hand	l-held, field
EFSA calculator	Potential exposure	0.2100	700.00
8 hours/day			
60 kg bodyweight	+ work wear	0.0750	250.00
TC:	(arms, body and legs covered)		
14000 cm <sup>2</sup> /hour (potential exp.)	+ work wear and gloves	0.0210	70.00
5000 cm <sup>2</sup> /hour (work wear)	<i>.</i>	0.0220	
1400 cm <sup>2</sup> /hour (work wear+gloves)			
1.0 % dermal absorption (in-use)			
0.9 % dermal absorption (conc.)			
Nursery stock plants (potted plants)*	*, application rate 1440 g a.i./ha,	vehicle mounted and hand	I-held downward
spraying, field			Т
EFSA calculator	Potential exposure	0.2419	806.40
8 hours/day			
60 kg bodyweight	+ work wear	0.0864	288.00
TC:	(arms, body and legs covered)		
$14000 \text{ cm}^2/\text{hour (potential exp.)}$	+ work wear and gloves	0.0242	80.64
5000 cm <sup>2</sup> /hour (work wear)			
1400 cm <sup>2</sup> /hour (work wear+gloves)			
3.0 % dermal absorption (in-use)			
0.9 % dermal absorption (conc.)			
Refined exposure considering a lowe	r dislodgeable foliar residue (DF	'R; 1.65 μg/cm <sup>2</sup> of foliage/k	دg a.i. applied/ha)
Golf greens, application rate 3750 g a	a.i./ha, vehicle mounted and han	d-held downward spraying	g, field
EFSA calculator	Potential exposure	0.04785	159.5
8 hours/day			

Model data	Level of personal protective equipment	Operator exposure [mg/kg bw/day]	% of <b>AOEL</b> <sup>1)</sup>
60 kg bodyweight	+ work wear	0.02063	68.75
TC:	(arms, body and legs covered)		
5800 cm <sup>2</sup> /hour (potential exp.)	+ work wear and gloves	0.004785	15.95
2500 cm <sup>2</sup> /hour (work wear)	6		
580 cm <sup>2</sup> /hour (work wear+gloves)			
1.0 % dermal absorption (in-use)			
0.9 % dermal absorption (conc.)			
Refined exposure considering shorte	er duration (4.5 h/day) in addition	n to a refined DFR-value	
Golf greens, application rate 3750 g	a.i./ha, vehicle mounted and han	d-held downward spraying	g, field
EFSA calculator	Potential exposure	0.02692	89.72
4.5 hours/day			
60 kg bodyweight	+ work wear	0.01160	28 68
TC:	+ work wear (arms, body and lags covered)	0.01100	30.00
5800 cm <sup>2</sup> /hour (potential exp.)	(arms, body and legs covered)		
2500 cm <sup>2</sup> /hour (work wear)	+ work wear and gloves	0.002692	8.97
580 cm <sup>2</sup> /hour (work wear+gloves)			
1.0 % dermal absorption (in-use)			
0.9 % dermal absorption (conc.)			

<sup>1)</sup> AOEL 0.03 mg/kg bw/day

As a conclusion the exposure estimations indicate that levels of exposure for operators, bystanders, residents and

workers will be within acceptable levels of the proposed systemic AOEL (or AAOEL where relevant) of

quinoclamine.

Note that possible exposure of workers in greenhouse and possible need for re-entry period for workers has not been assessed.

### 2.7 Residues

### 2.7.1 Summary of storage stability of residues

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.2 Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.3 Definition of the residue

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.4 Summary of residue trials in plants and identification of critical GAP

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.5 Summary of feeding studies in poultry, ruminants, pigs and fish

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.6 Summary of effects of processing

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.7 Summary of residues in rotational crops

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.8 Summary of other studies

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.9 Estimation of the potential and actual exposure through diet and other sources

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.10 Proposed MRLs and compliance with existing MRLs

Not relevant for the proposed representative uses of Quinoclamine.

### 2.7.11 Proposed import tolerances and compliance with existing import tolerances

Not relevant for the proposed representative uses of Quinoclamine.

### 2.8 Fate and behaviour in the environment

### 2.8.1 Summary of fate and behaviour in soil

### 2.8.1.1 Route and rate of degradation in soil, laboratory studies

Sufficient laboratory data were presented on the fate and behaviour of quinoclamine and its degradation products in soil. Evaluation of the studies is presented in Vol 3, B.8 (CA).

Degradation of quinoclamine in soil under aerobic standard conditions was investigated in two studies (Völkel, 2015 and Muttzall & Vonk, 1992). A third study (Lewis, 2003a) investigated degradation at 10°C but is considered to provide only supportive information. One study carried out under anaerobic conditions (Lewis, 2003b) was available and two studies on photochemical transformation at the soil surface (Adam, 2016a and Bishop, 2003) of which the older study is considered to provide only indicative information. Separate laboratory studies on rate of degradation of photochemical transformation products were submitted (Adam, 2016b, Piskorski, 2016, Fiebig, 2016 and Fiebig, 2017). For new studies, the kinetic assessments were generally done as part of each study report. For old studies, new kinetic assessments were generally provided as separate reports. Originally, the applicant suggested that the old studies on aerobic soil degradation (Muttzall & Vonk, 1992) and soil photolysis (Bishop, 2003) were unreliable since bound residues were evaluated insufficiently. The RMS nevertheless requested the old studies together with new kinetic data. Following evaluation the RMS concluded that there was no generally applicable reason not to consider the old studies.

Völkel (2015) incubated quinoclamine at 20.3°C for 142 days in four soils at a relatively high test concentration of 9.8 mg/kg, corresponding to 7350 g/ha (0-5 cm, 1.5 g/cm<sup>3</sup>). Samples were extracted four times with acetonitrile:water (4:1) and additionally by Soxhlet extraction with acetonitrile:water (4:1) for four hours. The non-extractable fraction increased over the course of the study. After 91 days it accounted for 11.4%, 17.3%, 23.8% and 17.1% AR in the four soils. After 142 days this had increased further to 17.8%, 22.0%, 25.9% and 23.7%, respectively.

By comparison, Muttzall & Vonk (1992) incubated quinoclamine at 20°C in four soils at 3 mg/kg, corresponding to 2250 g/ha (0-5 cm, 1.5 g/cm<sup>3</sup>). Mass balance was only established for two of the soils. Final samples were taken after 100 days, except for two of the soils in which extractable radioactivity and amounts of quinoclamine were determined also after 129 days. Samples were extracted in methanol and the extraction repeated until the last extract contained  $\leq$  5% AR. One of the soils was finally extracted with water. In the two soils for which mass balance was established, the non-extractable fraction increased until sampling day 78, at which 37.8% and 43.6% were non-extractable. After 100 days the corresponding amounts were slightly lower at 34.1% and 43.5%, respectively.

In comparison, extraction was apparently more complete in Völkel (2015). Rate of degradation was also considerably longer in Völkel (2015). However, the more rapid degradation in the old study (Muttzall & Vonk, 1992) was shown not only as loss of parent compound (which in part may have been due to poor extraction) but also in higher amounts of <sup>14</sup>CO<sub>2</sub>. In the four soils used by Völkel (2015) <sup>14</sup>CO<sub>2</sub> accounted for 12.7%, 21.1%, 31.7% and 19.7% after 91 days. After 142 days this had increased further to 23.6%, 28.0%, 44.6% and 35.1%, respectively. In Muttzall & Vonk (1992) <sup>14</sup>CO<sub>2</sub> accounted for 43.4% and 35.9% after 100 days. Comparison of the results from days 91 and 100, respectively, suggests that mineralisation was lower in at least three of the soils used by Völkel (2015). The reasons for the slower degradation observed in Völkel (2015) are not known but it cannot be excluded that the relatively high test concentration was one of them. Dose dependent degradation was suggested by the results from the study on aerobic mineralisation in surface water (Völkel, 2016a). Assuming 90% crop interception for the use on golf greens and 50% interception for the use in nurseries a single application would result in 0.54-4.5 mg/kg (0-5 cm, 1.5 g/cm<sup>3</sup>). The test concentration used by Muttzall & Vonk (1992) falls within this range whereas the test concentration used by Völkel (2015) was about twice as high as the upper end of the range. The results from Völkel (2015) may therefore potentially be less representative but there may be additional unknown reasons for the slower degradation rate. On balance, the RMS concluded that the results from both studies should be relied upon.

Muttzall & Vonk (1992) extracted soils with methanol, not followed by Soxhlet extraction. In some of the other soil studies where methanol was used for extraction, this was followed by Soxhlet extraction (Lewis 2003a and 2003b, Adam, 2016a, and Bishop, 2003). In those studies Soxhlet released additionally 3.9-9.6% AR. These are relatively minor amounts and it is not likely that the in-complete extraction in Muttzall & Vonk (1992) had a dramatic effect on the observed degradation rate. It is also not considered likely that all radioactivity that potentially could have been released in Soxhlet would consist of only one or two metabolites which may have been missed due to the in-complete extraction.

Depending on soil, Völkel (2015) observed one-four identified metabolites in the extracts: phthalic acid, 2-carboxybenzaldehyde, AN (2-amino-1,4-naphthalenedione) and AHN (2-amino-3-hydroxy-1,4naphthalenedione). Maximum amount of individual metabolite was 2.8% AR (phthalic acid). Additional five minor metabolites were occasionally observed at even lower amounts. Muttzall & Vonk (1992) observed at least five metabolites which in total accounted for maximum 6% AR and individually maximum 4% AR. Two of the metabolites were identified as HN (2-hydroxy-1,4-naphthalenedione, max 2% AR) and DHN (1,4dihydronaphthalenedione, max 1% AR). One additional polar metabolite (max ca 2% AR) was observed in the water extract of one of the soils.

One of the soils used by both Völkel (2015) and Muttzall & Vonk (1992) was "Speyer 2.2" however with slight difference in composition and therefore treated as different soils herein. Lewis (2003a) also used "Speyer 2.2" for incubation at 10°C and the soil characteristics deviated more for this sample of the soil. Lewis (2003a) extracted twice with methanol and twice with water and at three sampling points additionally with Soxhlet extraction (methanol:water, 2:1). Soxhlet released 5.8-7.3% AR. At sampling point 90 days, at which Soxhlet was not used,

24.3% AR was non-extractable. At sampling point 120 days, 18.4% was non-extractable and 7.3% AR was found in Soxhlet extracts. <sup>14</sup>CO<sub>2</sub> accounted for 37.9% AR by day 90, 42.3% AR by day 120. Metabolites AN (2-amino-1,4-naphthalenedione) and HCN (2-chloro-3-hydroxy-1,4-naphthalenedione) were observed as <1% AR each. Additionally, un-identified metabolites accounted for total 5.7% AR after 120 days. Lewis (2003a) used a test concentration of 3.75 mg/kg, corresponding to 2810 g/ha (0-5 cm, 1.5 g/cm<sup>3</sup>), thus within the representative range. Since incubations at 10°C are not required anymore Lewis (2003a) is considered only to provide supportive information.

Rate of degradation in the studies by Völkel (2015) and Muttzall & Vonk (1992) is summarised in the below table. There was no indication of pH-dependency of the degradation rate. For Lewis (2003a) the RMS calculated a  $DT_{50}$  of 43.0 days at 10 °C (SFO, Chi2 error 8.0%, based on methanol extracts).

Table 2.8.1.1-1. Summary of kinetic evaluation of laboratory data on aerobic degradation of quinoclamine in soil (from Völkel, 2015 and Knopp & Böing, 2016a kinetic re-assessment of results in Muttzall & Vonk, 1992).

Study	Soil		best-fit	DT50 / DT90,	w <b>2</b>	Modelling endpoint (20°C, pF 2)	
	5011	рп	model	days	χ2, error- %	DT50, days	kinetic model
	Soil I Speyer 2.1 sand	5.0 <sup>a</sup>	SFO	196 / 652	4.4	202	SFO
Välkal 2015	Soil II Speyer 2.2 loamy sand	5.5 ª	DFOP	154 / 743	2.8	149	SFO
Völkel, 2015	Soil III Speyer 2.4 loam	7.2 ª	SFO	77.1 / 256	1.4	79	SFO
	Soil IV Speyer 5M sandy loam	7.3 <sup>a</sup>	SFO	117 / 390	2.8	120	SFO
	Speyer 2.2 loamy sand	5.5 <sup>b</sup>	SFO	23.9 / 79.5	2.9	23.9	SFO
	Loam soil loam	7.3 <sup>b</sup>	SFO	33.7 / 112.1	8.9	30.3	SFO
Muttzall & Vonk, 1992	Humic sand soil sand	5.2 <sup>b</sup>	SFO	34.1 / 113.4	3.2	34.1	SFO
	Sandy loam soil sandy loam	7.5 <sup>b</sup>	SFO	19.1 / 63.5	3.4	18.3	SFO
Geometric mea	an, days					58.0	

a In CaCl<sub>2</sub>.

b In KCl.

Under anaerobic conditions (Lewis, 2003b) quinoclamine declined rapidly but mainly into non-extractable residues (80.1% AR after 120 days) whereas mineralisation was low, only 0.7% AR <sup>14</sup>CO<sub>2</sub> after 120 days. Additionally, metabolites were observed in higher quantities than under aerobic conditions. These were identified as AN (max 14.6% day 14), DHN (max 6.0% day 14) and, at lower levels, HN, HCN and AHN. In this study samples were extracted twice with methanol and twice with water and at three sampling points additionally with Soxhlet extraction (methanol:water, 2:1). Soxhlet released 4.3-9.6% AR. The RMS re-calculated degradation rates

for quinoclamine and metabolite AN (based on methanol extracts).  $DT_{50}$  for the parent was 3.9 days (SFO, Chi2 error 9.3%) and  $DT_{50}$  for the metabolite was 4.0 days (SFO-SFO, Chi2 error 21.4%). Anaerobic conditions are not considered relevant for the representative use, with applications in spring or summer.

Photolysis at the soil surface was investigated under laboratory conditions (Adam, 2016a). Samples were continuously irradiated for up to 17 days, corresponding to 31.1 days of natural summer sunlight at latitudes 30 to 50°N. Samples were extracted twice with methanol, twice with water and thereafter by Soxhlet extraction (methanol:water, 1:1). By the end of the study, non-extractable residues had reached 14.8% AR, and  $^{14}CO_2$  21.1%. Up to 19 transformation products were observed. Major products were phthalic acid (M6, max observed 20.4%), phthalamic acid (M9, max 9.0%), 2-oxalyl-benzoic acid (M10, max 10.6%) and 2-amino-oxalyl-benzoic acid (M11, max 5.3%). Remaining products were individually observed as max 3.1% AR. Quinoclamine was stable in dark controls. Under the conditions of the test  $DT_{50}$  for quinoclamine was calculated to 6.9 days (SFO, Chi2 error 2.8%). This would correspond to  $DT_{50}$  12.6 days of natural summer sunlight at 30 to 50°N. Hence, photolysis may significantly contribute to the degradation of quinoclamine under field conditions.

There was also an old study on photolysis on soil (Bishop, 2003). There were three un-identified products observed in this study (SP3, SP6 and SP7), individually accounting for max 5.3% AR by study end. Degradation of quinoclamine was slow; the parent accounted for ca 62% AR after 15.8 days of continuous irradiation, corresponding to 31 days of natural summer sunlight in the UK. Knopp & Böing (2016b) re-calculated the DT<sub>50</sub> for the parent to 57.8 days and the DT<sub>90</sub> to 322 days (DFOP, Chi2 error 1.0%) for the conditions of the test (continuous irradiation). Since >50% of the parent was still present by study end the estimated degradation rate is considered uncertain. Since both route and rate of photochemical transformation on soil was better described in the new study (Adam, 2016a) the old study is considered as indicative only.

The rate of degradation of the four main photolysis-products was investigated in separate studies. They all degraded very fast, see tables below. For M6 (Adam, 2016b) there was a relatively high variation between replicates which presumably was the reason for relatively high Chi2 error-%. For M9 (Piskorski, 2016) the RMS noted that recovery in freshly fortified samples were low (50.8-76.5%) and the  $DT_{50}$  is therefore considered as uncertain. However, there was no trend in the recoveries of the fortified samples and therefore it is unlikely that correction for these recoveries would result in a more conservative  $DT_{50}$  (out of six sampling points the lowest recoveries were observed in the second and third).

Table 2.8.1.1-2. Summary of kinetic evaluation of laboratory data on aerobic degradation of photochemical transformation product phthalic acid (M6) in soil (from Adam, 2016b).

Study	Soil	рН	best-fit model	DT50 / DT90, days	χ2, error-%	Modelling endpoint (20°C, pF 2)	
						DT50, days	kinetic model
Adam, 2016b	Soil I Speyer 2.1 sand	4.9 <sup>a</sup>	SFO	1.0 / 3.5	14.3	1.0	SFO
	Soil II Speyer 2.4 loam	7.3 ª	SFO	0.35 / 1.2	20.8	0.35	SFO
	Soil III Speyer 5M sandy loam	7.3 ª	SFO	0.58 / 1.9	18.9	058	SFO
Geometric mea	an, days			•		0.6	

a In CaCl<sub>2</sub>.

 Table 2.8.1.1-3.
 Summary of kinetic evaluation of laboratory data on aerobic degradation of photochemical transformation product phthalamic acid (M9) in soil (from Piskorski, 2016).

Study	Soil	рН	best-fit model	DT50 / DT90, days	χ2, error-%	Modelling endpoint (20°C, pF 2)	
						DT50, days	kinetic model
Piskorski, 2016	Soil I Speyer 2.1 loamy sand	4.9 ª	SFO	1.1 / 3.5	9.6	1.1	SFO
	Soil II Speyer 2.4 loam	7.4 ª	SFO	0.31 / 1.0	12	0.31	SFO
	Soil III Speyer 5M sandy loam	7.3 ª	SFO	0.39 / 1.3	7.0	0.39	SFO
Geometric mea	an, days	•	•	•		0.5	

a In CaCl<sub>2</sub>.

 Table 2.8.1.1-4.
 Summary of kinetic evaluation of laboratory data on aerobic degradation of photochemical transformation product M10 in soil (from Fiebig, 2016).

Study	Sou	Soil pH	best-fit	DT50 / DT90,	χ2, error-%	Modelling endpoint (20°C, pF 2)	
	501		model	days		DT50, days	kinetic model
	LUFA 2.2 sandy loam	5.4 ª	SFO	0.13 / 0.43	10.4	0.13	SFO
Fiebig, 2016	LUFA 2.3 sandy loam	5.9 ª	SFO	0.30 / 0.99	14.2	0.25	SFO
	LUFA 2.4 loam	7.4 <sup>a</sup>	SFO	0.17 / 0.57	8.6	0.15	SFO
Geometric me	an, days					0.2	

a Media not reported.

Study	Soil	best-fit		DT50 / DT90,		Modelling endpoint (20°C, pF 2)	
		рп	model	days	χ <b>2, error-</b> 76	DT50, days	kinetic model
Fiebig, 2017	LUFA 2.2 sandy loam	5.4 ª	SFO	0.54 / 1.8	9.4	0.54	SFO
	LUFA 2.3 sandy loam	5.9 ª	SFO	1.1 / 3.7	5.0	1.0	SFO
	LUFA 2.4 loam	7.4 <sup>a</sup>	SFO	0.67 / 2.2	6.1	0.58	SFO
Geometric mea	an, days					0.7	

Table 2.8.1.1-5. Summary of kinetic evaluation of laboratory data on aerobic degradation of photochemical transformation product M11 in soil (from Fiebig, 2017).

a Media not reported.

#### 2.8.1.2 Rate of degradation in soil, field studies, and modelling endpoint

A new field dissipation study (Janßen, 2017) was submitted together with a storage stability study (Dautel, 2017). Old field dissipation data included Beinhauer (1997) with residue analyses in Brielbeck (1997a and b). Kinetic evaluations of all field data were done in separate reports.

The new field study (Janßen, 2017) was carried out at two field sites in Germany; Weeze in North Rhine-Westphalia (Trial 01) and Gerichshain in Saxony (Trial 02). The soils were prepared as for sowing and then left fallow. Glyphosate was applied to keep the plots free of vegetation. The field phase of the study started in August 2015 when the test substance was applied. Mogeton Top WG formulation was sprayed onto the soil surfaces at a rate of 7500 g/ha corresponding to 3750 g quinoclamine/ha (nominal). Three replicate sub-plots (A, B, C) were used at each trial site, and these were further divided into 17 "subsub-plots" each. At each sampling interval ten soil cores were taken from each treated sub-plot A-C, to a depth of 1.0 m (10 cm on day 0). Within max 6 hours after sampling, soil cores were segmented (10 cm segments), pooled and freezed. Soil samples were extracted with acetonitrile:water (1:1), and soil segments were analysed until residues of quinoclamine were less than LOD. No metabolites were included in the analyses. LOQ was  $2 \mu g/kg$  and LOD 0.72  $\mu g/kg$ . LOQ represented 0.04% of the nominal dose, and 0.05-0.07% of the maximum residues found. Samples were taken from the plot until day 113 (Trial 01) and day 206 (Trial 02). In the storage stability study (Dautel, 2017) stability (>80%) was demonstrated over 3 months storage at temperature  $\leq$  -18°C. Thereafter stability decreased to 67.5% after 6 months, and 63.6% after 9 months. In the field study samples from the first sampling points were stored longer than 3 months; at Trial 01 samples from days 0-30 were stored for 116-154 days before analyses, and at Trial 02 samples from days 0-60 were stored for 105-182 days. Hence some degradation of quinoclamine in those samples cannot be excluded. If so, the actual residues from the early sampling dates may have been higher than the measured concentrations. The effect of this would be that the DT<sub>50</sub>s calculated may be longer (i.e., more conservative) than what they would have been if the samples would have been stable during storage.

Residues of quinoclamine were predominantly found in the upper 20-cm soil horizon. Residue levels expressed as  $\mu g/kg$  were converted into g/ha and the total residues in 0-40 cm soil calculated. Knopp (2017a) provided the kinetic analyses. DisT<sub>50</sub>s were calculated using non-normalised data from all sampling points to 7.6 days at Trial 01 (SFO, Chi2 error 22.9%) and to 8.6 days at Trial 02 (SFO, Chi2 error 9.8%). DegT<sub>50/90</sub> were calculated using time-step normalised data from all sampling points and DegT<sub>50/90, matrix</sub> were calculated using time-step normalised data from sampling points after cumulative rainfall of >10 mm. At Trial 01, more than 10 mm rain had fallen before sampling day 2 (normalised to sampling day 1.5). At Trial 02, more than 10 mm rain had fallen before sampling day 15 (normalised to sampling day 14.2). In the table below the results after omitting the first sampling points are shown (i.e., DegT<sub>50/90, matrix</sub>).

There was also an old field study available (Beinhauer, 1997 and Brielbeck & Marx, 1997a and b). Four German field sites were included but considering the representative use only the two trials in which application was made in the spring are considered here. These sites were located in Gnaschwitz, Saxony and Rostock, Mecklemburg. Mogeton 25WP was sprayed onto the bare soil surfaces at the end of May, 1996, at a rate of 15 kg/ha, corresponding to 3750 g quinoclamine/ha. There was one treated plot per site. Samples were taken until 150-152 days after application. Twenty soil cores per plot were taken to a depth of 20 cm, segmented, pooled and kept frozen until analyses. Soil samples were extracted twice with acetone:water (2:1). LOQ was 0.02 mg/kg, representing 0.5% of the nominal dose and 0.6-2% of the maximum residue observed. LOD was not stated. No metabolites were included in the analyses.

At Gnaschwitz, residues were only found in the 0-10 cm soil layer, whereas at Rostock site, residues were determined in the 10-20 cm layer on sampling days 0-28. The total residues in the 0-20 cm layer were used for the kinetic analyses for Rostock. The RMS calculated DisT<sub>50/90</sub> using non-normalised data from all sampling points. DisT<sub>50</sub> at Gnaschwitz was 7.9 days (SFO, Chi2 error 6.8%) and at Rostock 9.2 days with DisT<sub>90</sub> 62.9 days (DFOP, Chi2 error 5.0%). As calculated from k2 in DFOP the DisT<sub>50</sub> was 24.6 days. Knopp (2017b) calculated DegT<sub>50/90</sub> using time-step normalised data from all sampling points and DegT<sub>50/90, matrix</sub> using time-step normalised data using only data from sampling points after cumulative rainfall of >10 mm. At Gnaschwitz, more than 10 mm rain had fallen already 1 day after application. Due to missing weather data, day lengths for June, 1996, were not normalised for the Gnaschwitz site, and the next sampling day (day 7) was also the starting point for the kinetic analysis. Additionally, data from Gnaschwitz could not be normalised with regard to moisture, hence field capacity was assumed at the site and in that respect the result may be conservative. At Rostock, more than 10 mm rain had fallen after day 7 (the next sampling date was day 14, normalised to day 15.1 which was the starting point for the kinetic analysis). In the table below the results after omitting the first sampling points are shown.

Table 2.8.1.2-1. Summary of kinetic evaluation of data on degradation of quinoclamine under field conditions, time-step normalised and using only sampling points after cumulative rainfall of >10 mm. From Knopp (2017a and b).

Study	G. 1	be be	best-fit	DT50 / DT90,	DT50 / DT90,	Modelling endpoint (20°C, pF 2)	
	5011	рп	model	(20°C, pF 2)	χ <b>2</b> , error- 76	DT50, days	kinetic model
Janßen, 2017	Trial 01, DE loamy fine sand	5.6 ª	SFO	4.5 / 15.0	29.1	4.5	SFO
	Trial 02, DE loam	6.6 <sup>a</sup>	HS	8.6 / 23.6	8.7	5.7	from k <sub>2</sub> in HS
Beinhauer, 1997 and	Gnaschwitz silt	5.4 ª	SFO	9.6/31.7	10.7	9.6	SFO
Brielbeck & Marx, 1997a and b	Rostock silt	5.9 ª	SFO	20.3 / 67.3	11.4	20.3	SFO
Geometric mea	an, days	•	•	·	·	8.4	

a In CaCl<sub>2</sub>.

 $DT_{50}$  for modelling input was determined after comparison of normalised laboratory and field  $DT_{50}$ s using the EFSA Endpoint selector. According to the current guidance the geometric mean of the field results should be used, i.e. 8.4 days.

### 2.8.1.3 Assessment in relation to the P-criteria for soil

The criteria for persistence in soil, as stated in Annex II to Regulation (EC) 1107/2009, are DT<sub>50</sub> 120 days (PBT) and 180 days (POP and vPvB). It is assumed that these criteria represent a constant rate of degradation over the decline curve, i.e. that single first order (SFO) kinetics has been assumed implicitly when the criteria were defined.

For quinoclamine, the laboratory  $DT_{50}s$  at 20°C were variable ranging from 19 to 196 days. Two of the eight laboratory  $DT_{50}s$  were above the criterion for P in PBT and one additional value was close to the criterion. One of the  $DT_{50}s$  were also above the criterion for vP and POP. Low extraction efficiency may have contributed to short  $DT_{50}s$  in four of the soils, and high test concentration may have contributed to long  $DT_{50}s$  in the other four soils. It is not considered likely that release of additional max. ca 10% in extracts from the laboratory study with low extraction efficiency would have resulted in  $DT_{50}s$  above the criteria. Four field  $DegT_{50, matrix}$  values were all clearly below the criteria. As an overall conclusion considering all available data, quinoclamine is not considered as a persistent or as a very persistent substance in soil.

### 2.8.1.4 Adsorption in soil

Two studies were available on adsorption of quinoclamine to soil. Brielbeck & Marx (1998) used two soils, and the experimental data from the study were corrected and re-calculated in accordance with guideline by Frauen & Stähler (2001). The second study (Lewis, 2000) used four soils. There was no indication of pH-dependency of adsorption over the range tested (4.0-7.6).

Table 2.8.1.4-1. Quinoclamine: Adsorption coefficient, Freundlich isotherm, Freundlich exponent ("1/n"). ( $K_F$  and  $K_{F,oc}$  at 1 mg/l)

Study	Soil	OC %	Soil pH	K <sub>d</sub> (mL/g)	K <sub>d,oc</sub> (mL/g)	K <sub>F</sub> (mL/g)	K <sub>F,oc</sub> (mL/g)	"1/n"
Frauen & Stähler, 2001 (Brielbeck & Marx, 1998)	Soil 1 Agroplan sandy loam	0.87	6.4 <sup>a</sup>	13.9	1598	11.37	1307	0.686
	Soil 2 Speyer 2.1 loamy sand	0.59	6.0 ª	4.2	712	4.79	812	0.805
Lewis, 2000	PT 102 sandy silt loam	2.8	6.7 <sup>b</sup>	14.87	531	16.63	594	0.810
	SK 961089 clay loam	4.7	7.6 <sup>b</sup>	24.07	512	25.95	552	0.838
	Speyer 2.1 sand	0.4	5.2 <sup>b</sup>	2.57	642	3.72	931	0.727
	SK 566696 sandy loam	0.8	4.0 <sup>b</sup>	6.27	784	7.92	990	0.763
Geometric mean						9.41	827	-
Arithmetic mean						-	-	0.772

a Medium not stated.

b In CaCl<sub>2</sub>.

There was also an adsorption study on the metabolite AN (Dardemann, 2010) available. There were several deviations from the OECD guideline and the study was not considered acceptable by the RMS. No other experimental studies on adsorption of metabolites/transformation products were submitted. In the absence of data, K<sub>F,OC</sub>/K<sub>F,OM</sub> should generally be set to zero in exposure modelling. However, for metabolite AN the RMS suggests that an estimated value of Koc 605.6 L/kg could be used as a surrogate endpoint in calculations of PECsw/sed. This value was estimated in KOCWIN v2.00, Kow method (Heimann, 2018). Metabolite AN was identified as a major metabolite only in sediment, and in soil only under anaerobic conditions. Anaerobic conditions in soil are not considered relevant for the representative use, with applications in spring or summer. Therefore the RMS has not identified experimental adsorption data as a data gap for metabolite AN. However, should anaerobic conditions be considered relevant for other representative uses, then it may be necessary to request further adsorption data for metabolite AN at Member State level.

### 2.8.2 Summary of fate and behaviour in water and sediment

This section has been written to present degradation data necessary for comparison with the CLP criteria as well as to fulfil the requirements under Regulation (EC) No 1107/2009. The comparison with the CLP criteria is presented in section 2.9.2.4.2 (Long-term aquatic hazard (including bioaccumulation potential and degradation)).

### 2.8.2.1 Rapid degradability of organic substances

An overview of all studies that are considered relevant for the aquatic compartment are summarised in the table below. The studies are further presented in the sections that follow. See Vol 3, B.8 (CA) for additional information. All key studies listed in the table are considered suitable for CLP.

Method	Results*	Key or Supportive study *	Remarks	Reference
Hydrolysis (OECD TG No 111)	Stable at pH 4 and 7 at 50°C. At pH 9 (50°C) the SFO DT <sub>50</sub> was 9 days, this was extrapolated to DT <sub>50</sub> 360 days (20°C). A single metabolite (HCN) was observed as 50% AR after 9 days at 50°C. Mineralisation was not measured.	Key study	No remarks. Quinoclamine is considered to be hydrolytically stable at environmentally realistic pH values and temperatures.	Lewis, 2001
Aquatic photolysis (SETAC, 1995)	Photo-chemical $DT_{50}$ was 2.2 days (pH 5 buffer, 20°, continuous irradiation) corresponding to 4.2 days of natural sunlight in the UK (54°N). Seven products were formed but none of them could be identified. Unknown products 2 and 5 were observed as >10% AR. Mineralisation was not significant (<1% AR).	Key study	Due to the presence of un- identified products a second study was requested for the previous review (2007). Considering all available data it is considered likely that Unknown 5 was identical to phthalic acid.	Yeomans, 2003
Aquatic photolysis (SETAC, 1995; Japanese MAFF guideline ID #2-6-2; US EPA 161-2)	Photo-chemical DT <sub>50</sub> was 14.1 days (pH 5 buffer, 25°, continuous irradiation) and 11.9 days (sterile pond water, pH 6.6, 25°, continuous irradiation). These results were re-calculated to DT <sub>50</sub> 3.0 and 42.9 days, respectively, for Tokyo spring conditions. Two products were identified as >10% AR; phthalic acid and 2-carboxybenzaldehyde. Mineralisation reached 2.4% AR after 11 days of continuous irradiation of the sterile natural pond.	Key study	The minor difference in DT <sub>50</sub> between the systems may reflect contributing effect of indirect photolysis in the natural water.	Shah, 2006

Table 2.8.2.1-1. Summary of relevant information on rapid degradability.

Method	Results*	Key or Supportive	Remarks	Reference
Withou	Results	study *	Kemurks	Kelefence
	Mineralisation was not measured in the pH 5 buffer.			
	The quantum yield			
	(dimensionless) was			
	calculated to $2.7 \times 10^{-6}$			
	(natural water) and 25 x 10°			
Position paper	From the arguments presented	Supportive study	-	Heimann, 2014
on identity of	it is considered likely that			
products	Unknown 5 (in Yeomans,			
formed in	2003) was identical to			
photolysis	Shah, 2006)			
Calculation of	Using data from Yeomans	Supportive study		Greenwood & Liney,
quantum yield	(2003) the quantum yield			2005
	(dimensionless) was calculated to $3.55 \times 10^{-5}$			
Ready	No significant $CO_2$ evolution	Key study	Test	Hemmink & Blom, 1992
biodegradability	was observed in bottles with	5 5	concentration	,
(Draft OECD	quinoclamine over 28 days.		(18 and 35	
TG No 301, 1990)	The reference substance		mg/L) was close	
1770)	72%.		water solubility	
	It was concluded that		(19.8 mg/L,	
	quinoclamine is not readily		20°C).	
	biodegradable.		A slight	
			of quinoclamine	
			was noted.	
Aerobic	Pelagic system was used, and	Key study	The results	Völkel, 2016a
in water (OFCD	two test concentrations;		dependency of	
TG No 309)	Mineralisation reached 29.5%		degradation.	
	AR (high dose) and 50.7%			
	(low dose) after 61 days			
	Nine metabolites were			
	observed. HCN was observed			
	as max 5.2% AR and 2-			
	chloro-1,4-dimethoxy-3-			
	observed as max 6.2% AR			
	(both on day 61, low dose).			
	The remaining seven			
	metabolites were individually			
	SFO DT <sub>50</sub> s were determined			
	to 30.6 days (low dose) and			
	121 days (high dose).	17 / 1		
Aerobic degradation in	Kiver and pond water/sediment systems were	Key study	of quinoclamine	v olkel, 2016b
water/sediment	used. Quinoclamine was		in the total	
(OECD TG No	relatively rapidly distributed		systems was	
308)	to the sediments, with SFO		relatively rapid	
	of 4.2 days (river system) and		observed as a	
	3.2 days (pond system). SFO		major	
	$DegT_{50}$ in the total systems		metabolite. This	
	were 7.0 days (river system) and 8.9 days (pond system)		indicates that	
	Eleven metabolites were		were partially	
	observed; M1 and M2 were		anaerobic since,	
Method	Results*	Key or Supportive study *	Remarks	Reference
--	--	---------------------------	---	----------------
	only identified as >5% AR once and not identified: M1 as max 8.4% on day 20, and M2 as max 4.8% also day 20. M3, identified as AN, was observed as max 13.2% AR in total systems on day 7, whereof >10% in the sediment. Remaining metabolites were individually observed as max 1.9% AR. For AN, SFO-SFO DegT50 in the total systems were determined to 22.7 days (river) and 47.8 days (pond). After 60 days (study end) mineralisation reached 25.7% AR in the river system, 11.8% AR in the pond system.		in soil, degradation was more rapid under anaerobic conditions as compared to aerobic and AN was observed as a major metabolite only under anaerobic conditions in soil. This does not invalidate the study (see § 2 of the OECD TG).	
Aerobic degradation in water/sediment (BBA guideline, Part IV, 5-1)	Ditch and river water/sediment systems were used. Again, quinoclamine was relatively rapidly distributed to the sediments, with SFO DisT <sub>50</sub> from the water phase of 2.6 days (ditch system) and 3.5 days (river system). SFO DegT <sub>50</sub> in the total systems were 6.5 days (ditch system) and 6.1 days (river system). AN was the only major metabolite observed (three additional metabolites never exceeded 1%). AN was observed as max 18% AR in total systems on day 7, and >10% only in the sediment phase. Kinetic fitting of the data for AN together with parent data did not return acceptable results. Therefore decline fits were done, with SFO DT <sub>50</sub> for the total systems estimated to 14.1 days (ditch system) and 8.6 days (river system). By study end (day 105) mineralisation had reached 15.5% AR (ditch system) and	Key study	As for the study above (Völkel, 2016b) the results indicate that the sediments were partially anaerobic.	Muttzall, 1993

\* Key or supportive with reference to CLH endpoints.

# 2.8.2.1.1 Ready biodegradability

A study on ready biodegradability was available (Hemmink & Blom, 1992). The study was conducted in accordance with Draft OECD TG No 301 "CO2 Evolution test" (1990). The reference substance (acetate) was significantly degraded within 14 days (72% degradation). No significant CO2 evolution was observed over 28 days in bottles with quinoclamine. Two test concentrations of quinoclamine were used, 18 and 35 mg/L. It was noted that part of the test substance remained un-dissolved in the medium (water solubility of quinoclamine is 19.8 mg/L, 20°C). Nevertheless, the conclusion that quinoclamine is not readily biodegradable is still considered valid, and the test is considered as relevant for the purpose of classification and labelling.

## 2.8.2.1.2 BOD5/COD

No BOD<sub>5</sub>/COD test was available.

## 2.8.2.2 Other convincing scientific evidence

Relevant data on abiotic degradation were available (hydrolysis, see 2.8.2.2.5 and aquatic photolysis, see 2.8.2.2.6).

Other data of relevance for classification and labelling were one study on biodegradation in surface water (see 2.8.2.2.1), two studies on biodegradation water/sediment (see 2.8.2.2.4). Additionally, studies on biodegradation in soil were available (see 2.8.1.1 for soil laboratory data and 2.8.1.2 for soil field data).

## 2.8.2.2.1 Aquatic simulation tests

Völkel (2016a) investigated rate of mineralisation in surface water (pelagic test, OECD TG NO 309). Two test concentrations were used and the results indicate the degradation may be dose dependent. The results from the low dose experiment are considered as more representative (more close to estimated PECsw) than the results from the high dose. At study end (day 61) mineralisation reached 29.5% AR at the high dose (100  $\mu$ g/L) and 50.7% AR at low dose (10  $\mu$ g/L). In sterile samples (dosed at 100  $\mu$ g/L) quinoclamine remained stable throughout the test. After 12 days, mineralisation of the reference substance (benzoic acid) reached 73.5% AR (control samples) and 62.1% (solvent control samples).

Nine metabolites were observed. HCN (2-chloro-3-hydroxy-1,4-naphthalenedione) was observed as max 5.2% AR and 2-chloro-1,4-dimethoxy-3-aminonaphthalene was observed as max 6.2% AR (both on day 61, low dose). The remaining seven metabolites were individually present only as <5% AR.

SFO DT<sub>50</sub>s were determined to 30.6 days (low dose, Chi2 error 6.9%) and 121 days (high dose, Chi2 error 1.7%).

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

Field dissipation studies on soil are presented in section 2.8.1.2 but these data are considered as less relevant for classification purpose since only primary degradation and no mineralisation were measured. There was no monitoring data available (see 2.8.4).

# 2.8.2.2.3 Inherent and enhanced ready biodegradability tests

Inherent or enhanced biodegradability tests were not provided.

## 2.8.2.2.4 Soil and sediment degradation data

Soil degradation data are presented in sections 2.8.1.1 (laboratory data) and 2.8.1.2 (field data).

Two water/sediment studies were available (Völkel, 2016b and Muttzall, 1993). Völkel (2016b) was carried out in accordance with OECD TG No 308 (2002). Muttzall (1993) referred to an older guideline from German authority; BBA guideline, Part IV, 5-1 (1990) but essentially followed the principles of the current OECD guideline. The applicant originally suggested that the old study on water/sediment (Muttzall, 1993) was unreliable since bound residues were evaluated insufficiently. The RMS nevertheless requested the old study together with new kinetic data. The RMS has concluded that the old study can be relied on.

In Völkel (2016b) mineralisation reached 25.7% AR in the river system and 11.8% AR in the pond system (both on day 60, study end). In Muttzall (1993) mineralisation reached 15.5% AR in the ditch system and 30.8% AR in the river system (both on day 105, study end). By day 56 (to allow a comparison with the shorter study duration of Völkel, 2016b) mineralisation was 18.8% in the ditch system and 27.4% in the river system.

In Völkel (2016b) sediments were extracted up to three times with acetonitrile:water (4:1) followed by Soxhlet extraction with the same solvent system. Soxhlet extraction released 3.9-12% AR. Muttzall (1993) extracted sediments once with acetonitrile and once with methanol. In comparison, this was a mild extraction. Non-extractable residues accounted for max 67.9% (river system) and 82.4% (pond system) by day 60 in Völkel (2016b). By comparison, non-extractable residues accounted for max 73.1% (ditch system) and 62.1% (river system) by day 56 in Muttzall (1993). By study end at day 105, these amounts had increased to 80.6% and 67.1%, respectively. The comparison of the results from days 56/60 did not indicate that bound residues were higher in Muttzall (1993) than in the new study and the RMS decided to rely on both studies.

Degradation was relatively rapid in these systems and AN (2-amino-1,4-naphthalenedione) was observed as the (sole) major metabolite. Based on a comparison with results from aerobic and anaerobic soil studies this suggests that the sediments were partially anaerobic. This is considered acceptable ("The aerobic test simulates an aerobic

water column over an aerobic sediment layer that is underlain with an anaerobic gradient." §2 in OECD TG No 308).

Table 2.8.2.2.4-1. Summary of kinetic evaluation of laboratory data on aerobic degradation of quinoclamine in total water/sediment systems (from Völkel, 2016b and Knopp & Böing, 2016c kinetic re-assessment of results in Muttzall, 1993).

S4 1	Soil	OC in sediment.	pH of	best-fit	DT50 /	χ2, error-	Modelling endpoint (20°C, pF 2)	
Study	5011	%	water	model	DT90, days	%	DT <sub>50</sub> , days	kinetic model
Völkel,	River system	1.2	8.0	SFO	7.0 / 23.4	12.9	7.0	SFO
2016b	Pond system	4.7	7.6	SFO	8.9 / 29.6	15.2	8.9	SFO
Muttzall,	Ditch system	4.5	8.6	SFO	6.5 /21.5	4.0	6.5	SFO
1993	River system	1.2	8.0	SFO	6.1 / 20.3	3.5	6.1	SFO
Geometric n	nean, days						7.2	

Table 2.8.2.2.4-2. Summary of kinetic evaluation of laboratory data on dissipation of quinoclamine from water phase in water/sediment systems (from Völkel, 2016b and Knopp & Böing, 2016c kinetic re-assessment of results in Muttzall, 1993).

Study	Soil	OC in sediment, %pH of waterbest-fit modelDT50 / DT90, daysχ2, error- %		best-fit model	DT50 /	χ2, error-	Modelling endpoint (20°C, pF 2)	
Study	501			%	DT50, days	kinetic model		
Völkel,	River water	1.2	8.0	SFO	4.2 / 13.9	4.9	n.a.	-
2016b	Pond water	4.7	7.6	SFO	3.2 / 10.5	6.1	n.a.	-
Muttzall,	Ditch water	4.5	8.6	SFO	2.6 / 8.8	9.4	n.a.	-
1993	River water	1.2	8.0	SFO	3.5 / 11.7	5.4	n.a.	-

n.a. Not applicable.

Table 2.8.2.2.4-3. Summary of kinetic evaluation of laboratory data on dissipation of quinoclamine from sediment phase in water/sediment systems (from Völkel, 2016b and Knopp & Böing, 2016c kinetic re-assessment of results in Muttzall, 1993).

Std	Soil	OC in sediment	pH of	best-fit	DT50 /	χ2, error-	Modelling endpoint (20°C, pF 2)	
Study	501	%	water	model	DT <sub>90</sub> , days	%	DT <sub>50</sub> , days	kinetic model
Völkel,	River sediment	1.2	8.0	SFO	7.4 / 24.7	18.3	n.a.	-
2016b	Pond sediment	4.7	7.6	SFO	8.4 / 28.1	17.0	n.a.	-
Muttzall, 1993	Ditch sediment	4.5	8.6	SFO	12.5 / 41.6	8.7	n.a.	-
	River sediment	1.2	8.0	SFO	11.6 / 38.5	5.0	n.a.	-

n.a. Not applicable.

Völkel (2016b) observed eleven metabolites in the river system and seven metabolites in the pond system. M1 (un-identified) was observed as max 8.4% AR on day 20 in the river system but never again above 5%. M2 (un-identified) was observed as max 4.8% AR also on day 20 in the river system. M3 (identified as AN) was observed as max 13.2% by day 7 in the river system, mainly in the sediment phase. Remaining metabolites were individually observed as max 1.9% AR.

Muttzall (1993) also observed AN as the only major metabolite; max observation was 18% in the river system on day 7, whereof 12% was found in the sediment, 6% in the water phase. Three additional minor metabolites were observed, but their amounts never exceeded 1% AR.

## 2.8.2.2.5 Hydrolysis

One study on hydrolysis of quinoclamine was available (Lewis, 2001). The study was carried out in accordance with OECD TG No 111 (1981). Study conditions were pH 4, 7 and 9, and temperatures 50 and 74°C. At pH 4 and 7 (50°C) <10% hydrolysis had occurred after 5 days and the study was terminated. At pH 9, the study was prolonged 14 days to enable estimation of  $DT_{50}$ . Under the conditions of the test the  $DT_{50}$  was 9 days, and this was extrapolated to 360 days at 20°C. A single hydrolysis product was identified as HCN (2-chloro-3-hydroxy-1,4-naphthalenedione). It accounted for 50% AR after 9 days at pH 9, 50°C. Quinoclamine is considered to be hydrolytically stable at environmentally realistic pH values and temperatures.

## 2.8.2.2.6 Photochemical degradation

Three relevant reports were provided to address photochemical transformation in water; two experimental studies (Yeomans, 2003, Shah, 2006), and one position paper (Heimann, 2014). Yeomans (2003) did not identify the products formed and therefore a second study (Shah, 2006) was requested during the previous review of quinoclamine. In Shah (2006) two major products could be identified. Heinemann (2014) was a position paper submitted for the purpose of renewal, aiming to clarify the identity of products that were un-identified in the experimental study by Yeomans (2003). Yeomans referred to a test protocol which lacks detailed descriptions (SETAC, 1995). Shah (2006) additionally referred to Japanese MAFF guideline ID #2-6-2 (2000) and US EPA guideline 161-2 (1982). However, both experimental studies were essentially carried out in accordance with standard procedures for this type of study, as described in OECD TG No 316 (2008), except that spectral properties and irradiance was measured using a spectroradiometer instead of using a chemical actinometer.

In Yeomans (2003) the photochemical half-life was 2.2 days (pH 5 and 20°C, continuous irradiation, SFO), corresponding to 4.2 days in natural sunlight 12 hours per day at UK irradiation conditions. In Shah (2006)  $DT_{508}$  were estimated to 14.1 days (pH 5 and 25°C, continuous irradiation, SFO) and 11.9 days (sterile natural pond water, pH 6.6, 25°C, continuous irradiation, SFO). These  $DT_{508}$  were estimated to correspond to 42.9 days and 36.5 days, respectively, under natural spring conditions in Tokyo.

In Yeomans (2003) seven distinct products were formed but none of them could be identified. Two of the products (Unknown 2 and 5) were observed as >10% AR and two additional products were observed as >5% AR at two consecutive sampling points (Unknown 1 and 4), see table below. One additional product (Unknown 6) was observed close to 10% AR at the very last sampling point. Photochemical transformation of quinoclamine would be expected to occur only at the near-surface layer of natural water bodies. In the presence of sediments the rate of disappearance from water is expected to be relatively rapid for quinoclamine (DisT<sub>50</sub> 3-4 days). Therefore it may

be relevant to consider the time taken for the unknown products to reach >5% AR and >10% AR in the test system, noting that number of UK summer days would be twice the number of sampling days. Considering this, the RMS propose that it can be considered as less likely that under environmentally realistic conditions at least Unknowns 1, 3, 4, 6 and 7 would be formed in amounts that would call for further consideration.

Table 2.8.2.2.6-1. Quinoclamine and major products formed in aquatic photolysis study (Yeomans, 2003). Continuous irradiation of quinoclamine in sterile pH 5 buffer (% of applied, single samples, except at zero time where duplicate samples were taken).

Days after application	0	1.1	2.8	3.9	5.0
Quinoclamine (26.1 min <sup>a</sup> )	95.7	78.3	48.5	30.2	5.0
Unknown 1	n.d.	n.d.	5.5	6.1	2.5
Unknown 2 (13.7 min <sup>a</sup> )	n.d.	2.9	10.6	12.0	17.1
Unknown 3	n.d.	2.3	1.1	2.9	4.2
Unknown 4 (15.1 min <sup>a</sup> )	n.d.	n.d.	3.1	6.0	6.6
Unknown 5 (16.0 <sup>a</sup> )	n.d.	1.7	7.6	9.8	18.9
Unknown 6 (16.6 <sup>a</sup> )	n.d.	n.d.	4.4	4.5	9.9
Unknown 7	n.d.	1.2	4.3	4.9	4.3

n.d. Not detected.

a Approximate retention times from LC-MS analyses using atmospheric pressure chemical ionisation (APcI) in the negative ion mode.

In Shah (2006), two products were identified, phthalic acid and 2-carboxybenzaldehyde, bot present as >10% AR. There were no other products formed as >10% AR or as >5% AR at two or more consecutive sampling points, see table below. It is not considered likely that the minor products observed would be formed in significant amounts under natural conditions since the systems were continuously irradiated for 11 days and since photochemical transformation would be expected to occur only at the near-surface layer of natural water bodies.

Table 2.8.2.2.6-2.	Quinoclamine :	and major	products	formed i	n aquatic	photolysis	study	(Shah,	2006).	Continuous
irradiation of quir	oclamine in sto	erile natura	al pond wa	ater (pH 6	5.6) and st	terile pH 5	buffer	(% of	applied,	average of
duplicate samples)	•									

			Days	after applic	ation		
	0	1	3	4	7	9	11
Natural pond water							
Quinoclamine (25.3 min <sup>a</sup> )	100.4	94.9	87.3	79.3	71.3	63.6	50.4
16.3 min <sup>a</sup>	n.d.	1.7	2.4	3.8	4.7	4.7	5.7
17.4 min <sup>a</sup>	n.d.	0.5	1.8	1.9	3.3	3.9	5.1
Phthalic acid (18.7 min <sup>a</sup> )	n.d.	0.8	1.7	2.8	4.4	4.4	6.3
2-Carboxybenzaldehyde (19.4 min <sup>a</sup> )	n.d.	1.8	5.0	9.3	13.2	14.8	19.5
22.1 min <sup>a</sup>	n.d.	n.d.	0.5	0.9	1.1	1.2	1.7
22.9 min <sup>a</sup>	n.d.	n.d.	0.6	1.0	1.7	1.5	2.6
pH 5 buffer							
Quinoclamine (25.3 min <sup>a</sup> )	98.4	92.6	80.1	76.9	64.2	65.0	55.7
16.3 min <sup>a</sup>	n.d.	1.0	1.9	1.5	1.7	1.5	1.1
Phthalic acid (18.7 min <sup>a</sup> )	n.d.	1.7	5.0	7.1	9.2	10.5	10.8
2-Carboxybenzaldehyde (19.4 min <sup>a</sup> )	n.d.	2.6	8.0	9.0	16.7	13.7	18.3
21.0 min <sup>a</sup>	n.d.	n.d.	1.9	2.3	2.3	2.4	2.8
22.1 min <sup>a</sup>	n.d.	n.d.	1.0	1.0	1.7	1.7	2.3
24.5 min <sup>a</sup>	n.d.	n.d.	n.d.	n.d.	1.4	1.3	2.3

n.d. Not detected.

a HPLC retention times.

Heimann (2014) presented arguments to clarify the identity of unknown products formed in the experimental photolysis studies, and to show that none of the products would contain the toxophore of quinoclamine. The intact quinone ring of quinoclamine was identified as an essential part of the toxophore. Based on the differences in

retention times of (on the one hand) quinoclamine and the reference substances and (on the other hand) the photolysis products formed, as well as on the molecular weights proposed for the unknown products (data from Yeomans, 2003) the RMS agrees that it can be concluded that the quinone ring structure was no longer present in the photo-transformation products formed (possibly with the exception of Unknown 4 for which a relatively high molecular weight was proposed in Yeomans, 2003).

Furthermore, from the inhibitory action of quinoclamine on plastoquinone, involved in photosynthesis, together with the comparison of aquatic ecotoxicity data between quinoclamine and two of its transformation products that has lost the quinone ring (phthalic acid and phthalamic acid) it is concluded that the quinone ring has an essential role in the toxicity of quinoclamine. Thus, it is considered likely that the major photo-transformation products had lost the toxophore.

Heimann (2014) proposed that Unknown 5 and 6 in Yeomans (2003) were identical to phthalic acid and 2carboxybenzaldehyde identified in Shah (2006). From Heimann's evaluation of the MS data the RMS finds it reasonable to assume that Unknown 5 was identical to phthalic acid but for Unknown 6 the RMS concludes that based on the available data it cannot be demonstrated with reasonable certainty that it was identical to 2-carboxybenzaldehyde. Furthermore, a proposed identity of Unknown 2 is considered as highly uncertain.

The RMS propose that three products formed in aquatic photolysis needs to be considered further: phthalic acid (= Unknown 5), 2-carboxybenzaldehyde and Unknown 2.

## 2.8.2.2.7 Other / Weight of evidence

No other data that could be of relevance for the classification and labelling were available.

### 2.8.2.2.8 Assessment in relation to the P-criteria for water and sediment

The criteria for persistence in water and sediment, as stated in Annex II to Regulation (EC) 1107/2009, are: Water: DT<sub>50</sub> 40 days (fresh water in PBT), 60 days (POP, marine water in PBT, and all water in vPvB), Sediment: DT<sub>50</sub> 120 days (fresh water sediment in PBT), 180 days (POP, marine sediment in PBT, and all sediments in vPvB).

Quinoclamine is hydrolytically stable. Aquatic photolysis may contribute to the degradation of the substance but due to adsorption, quinoclamine is expected to remain near the surface of water bodies only for a limited period of time. In the study on aerobic mineralisation in surface water the  $DT_{50}$  of 121 days at the high test concentration (100 µg/L) was above the criteria for persistence in PBT as well as POP and vPvB. At the low test concentration (10 µg/L) the  $DT_{50}$  of 30.6 days was below the criteria. The RMS suggest that the result from the low test concentration are more relevant than the result from the higher dose since the low test concentration was more close to the estimated PECsw at Step 3 and above. In the water/sediment studies all  $DT_{50}$ s for degradation in the

total systems (7.0-8.9 days) were below the criteria. In this case, it may be more relevant to compare these results with the criteria for sediment (since quinoclamine is expected to partition to sediment relatively rapidly) but this makes no difference with regard to the conclusion regarding the criteria for persistence. The RMS concludes that the half-lives of quinoclamine does not exceed the criteria for persistence in the aquatic environment.

## 2.8.3 Summary of fate and behaviour in air

Quinoclamine has a vapour pressure of 3 x  $10^{-6}$  Pa ( $20^{\circ}$ C). This is below the trigger for further assessment as provided in FOCUS Air report (2007). Henry's Law constant was calculated to  $3.05 \times 10^{-5}$  Pa x m<sup>3</sup> x mol<sup>-1</sup>. This also indicates a low tendency for volatilisation from moist surfaces. Atmospheric half-life for reaction with hydroxyl radicals was estimated to 5.5 hours assuming an average daily air concentrations of hydroxyl radicals of  $1.5 \times 10^{6}$ /cm<sup>3</sup> (12-hr day). The RMS concludes that no further data on fate of quinoclamine in air is required.

## 2.8.3.1 Hazardous to the ozone layer

There were no data available on the potential hazard to the ozone layer.

## 2.8.3.1.1 Short summary and overall relevance of the provided information on hazards to the ozone layer

There were no data available on the potential hazard to the ozone layer.

## 2.8.3.1.2 Comparison with the CLP criteria

A comparison with CLP criteria cannot be made for the hazard class in question, i.e. hazardous to the ozone layer.

## 2.8.3.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

Due to lack of data no classification is proposed on classification and labelling for hazards to the ozone layer according to the CLP criteria.

# 2.8.4 Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

The applicant stated that no environmental monitoring data were identified in the literature search and no further data were provided. Quinoclamine is not included in the Swedish monitoring program at the national level. The RMS also searched for data in the Swedish regional pesticide database but there were no findings reported. Hence, no relevant monitoring data were available.

## 2.8.5 Definition of the residues in the environment requiring further assessment

Substances for which further exposure/risk assessment is considered necessary are listed in the below table.

It may be noted that under anaerobic conditions (flooded soil) AN (2-amino-1,4-naphthoquinone) and DHN (1,4dihydronaphthalene) were observed as >10% AR or as >5% at two consecutive sampling points, respectively. Considering the representative use for quinoclamine with timing of applications in April-August further assessment of AN and DHN as soil metabolites has not been requested. However, should application of quinoclamine in autumn/winter be considered for other areas of use, the RMS recommends that exposure/risk assessment should be presented for AN and DHN.

2.8.5-1. Definition of the residues in the environment requiring further assessment.

Compartment	Residue	Justification
	quinoclamine	by default
	phthalic acid (M6)	soil photolysis: max 20.4% AR
Soil	phthalamic acid (M9)	soil photolysis: max 8.8-9.0% AR at 2 consecutive points
	2-oxalyl-benzoic acid (M10)	soil photolysis: max 10.6% AR
	2-amino-oxalyl-benzoic acid (M11)	soil photolysis: max 5.2-5.3% AR at 2 consecutive points
	quinoclamine	by default
	phthalic acid (M6)	from soil
Groundwater	phthalamic acid (M9)	from soil
	2-oxalyl-benzoic acid (M10)	from soil
	2-amino-oxalyl-benzoic acid (M11)	from soil
	quinoclamine	by default
	phthalic acid (M6) (unknown 5)	from soil, additionally from aquatic photolysis: max 18.9% AR
	phthalamic acid (M9)	from soil
Surface water	2-oxalyl-benzoic acid (M10)	from soil
	2-amino-oxalyl-benzoic acid (M11)	from soil
	unknown 2	aquatic photolysis: max 17.1% AR
	2-carboxybenzaldehyde	aquatic photolysis: max 19.5% AR
	quinoclamine	by default
	phthalic acid (M6)	from soil
Sadimant	phthalamic acid (M9)	from soil
Seument	2-oxalyl-benzoic acid (M10)	from soil
	2-amino-oxalyl-benzoic acid (M11)	from soil
	2-amino-1,4-naphthoquinone, AN	water/sediment: max 18% AR of which 12% AR in sediment
Air	quinoclamine	by default

## 2.8.6 Summary of exposure calculations and product assessment

# 2.8.6.1 Summary of calculations of PECsoil

Acceptable PECsoil were calculated for quinoclamine and four transformation products formed in soil photolysis study: M6, M9, M10 and M11. PECsoil, plateau was not required for any of the substances.

PECsoil were calculated using the standard equations and assumptions, for the following areas of use:

Golf greens, single application of 3750 or 1875 g/ha,

Nursery stock plants, single application of 3750, 1875, 1440 or 810 g/ha.

For golf greens 90% crop interception was assumed, and this was justified by the dense grass on greens, with grass blades horizontally situated. For nursery stock plants 50% crop interception was assumed. This was considered as a realistic worst case since the substrate in the pots is expected to bind quinoclamine due to its high content of organic matter and since pots are normally placed close to each other with nearly 80%, or at least 50%, of the ground occupied by pots. For hand-held applications, it was added that the operator will target the application to the substrate surface of the pots.

# 2.8.6.2 Summary of calculations of PECgw

Acceptable PECgw were calculated for quinoclamine and four transformation products formed in soil photolysis study: M6, M9, M10 and M11. Standard modelling with PELMO, PEARL and MACRO was done. The transformation products were modelled separately, i.e. applied as parent substance with application rate corrected for molecular weight and formation. Due to misunderstandings in the communication between the RMS and the applicant, 25% formation of each metabolite was assumed for correction of the application rate. This is conservative since the maximum observed of these products was 20.4% (M6).

Worst case PECgw were calculated for the following areas of use: Golf greens, single application of 3750 g/ha, Nursery stock plants, single applications of 3750 g/ha.

"Grass/alfalfa" and "Beans (field)"/"Beans (vegetables)" were used as model crops, respectively.

Three different dates for application were considered: 1 April, 1 June and 1 August.

The application rates were corrected for crop interception and each substance applied to soil surface in the models. Crop interception was assumed to be 90% for golf greens and 50% for nursery stock plants (for justification, see above, PECsoil).

PECgw (80<sup>th</sup> percentile over 20 years simulation, 1 m depth) were calculated to  $\leq 0.000 \ \mu g/L$  for all compounds.

## 2.8.6.3 Summary of calculations of PECsw and PECsed

PECsw/sed were calculated at Steps 1-2 for quinoclamine, AN, M6, M9, M10, M11, 2-carboxybenzaldehyde and Unknown 2.

At Steps 3, 3b and 4 acceptable PECsw/sed were available for quinoclamine. The endpoints used for the parent deviated slightly from the final endpoints but the RMS accepted the modelling since the deviations were minor or resulted in more conservative estimates of exposure.

By contrast, the calculations done for metabolites and transformation products were not considered acceptable by the RMS. This was due both to approaches used and to choice of input values at Steps 3, 3b and 4.

Hence, a number of data gaps were identified:

- PECsw/sed at Steps 3, 3b and 4, as necessary, for metabolite AN using acceptable endpoints as input,

- PECsw/sed at Steps 3, 3b and 4, as necessary, for transformation products formed in soil photolysis. The RMS propose that these should be applied as parent substances with application rate corrected for molecular weight and % maximum observed in the soil photolysis study, and with spray drift excluded. Based on current results at Step 2 no further modelling would be required for M10.

- PECsw/sed at Steps 3, 3b and 4, as necessary, for transformation products formed in aquatic photolysis. The RMS propose that these PECsw could be calculated from the PECsw for the parent with correction for molecular weight and % maximum observed in the aquatic photolysis studies. It was noted that for M6, PECsw from formation on soil would need to be added to the PECsw from formation in water.

- The RMS understands that generating all these PECsw/sed for the metabolite and transformation products is work intense but depending on the outcome of the risk assessment, it may not be necessary to provide PECsw/sed for all use scenarios.

Step 3b was proposed by the applicant as a standard scenario for this crop/product combination. The RMS agrees that the standard FOCUS scenarios may be less relevant for uses on golf greens and nursery stock plants (potted plants) and that modifications of the standard assumptions may be necessary.

For use on golf greens, PECsw/sed was reduced at Step 3b by the following means:

- loading of streams from upstream catchment was excluded, since two golf courses would not be located that close to each other (less than 5 km),

- drainage was reduced due to small size of the treated area, hence loading by drainage was reduced by 90% for tractor drawn applications and by 97.5% for hand-held spot treatment,

- run-off was reduced since applications will only be made to grass surrounded by grass in fairway and rough. The fractional reduction in run-off volume and flux and in erosion mass and flux was 0.9 for tractor drawn applications and 0.975 for hand-held applications.

Additionally at Step 4 the following risk reduction was assumed for the golf green scenario at Step 4:

- spray drift was reduced by 95% nozzle reduction,

- run-off was further reduced by assumption of a 20 m vegetated buffer zone (fractional reduction 0.98/0.995 for tractor drawn applications, and 0.995/0.99875 for hand-held applications).

For applications to nursery stock plants in greenhouses, there was no drift loading assumed at Step 3b and no runoff assumed (only D-scenarios run).

At Step 4, 95% nozzle reduction was assumed, and 20 m vegetated buffer (fractional reductions for tractor drawn as well as hand-held applications were 0.8/0.95).

The RMS noted that the reductions assumed go beyond the limits recommended in the FOCUS Landscape and Mitigation report but the RMS accepted the applicant's justifications for the approach.

# 2.9 Effects on non-target species

## 2.9.1 Summary of effects on birds and other terrestrial vertebrates

## 2.9.1.1. Birds

The available data on avian toxicity of technical and formulated Quinoclamine are summarised in the table below, with toxicity data used for the risk assessment marked in bold.

Since the available avian short-term dietary LDD50 (394 mg a.s./kg bw/day) is lower than the acute oral LD50 (> 2000 mg a.s./kg bw), the dietary toxicity has to be considered in the acute risk assessment in accordance with the Guidance Document on Risk Assessment for Birds and Mammals (EFSA 2009/1438).

Species	Test substance	Time scale	Endpoint	Toxicity (mg a s /kg	Remarks	Reference
	substance			b.w./day)		
Bobwhite quail	Quinoclamine	Acute oral	LD50	> 2000	LD50 > highest dose tested	Anonymous 36 1986 Report 6025-602 (In DAR 2007)
Bobwhite quail	Mogeton 25% WP	Acute oral	LD50	> 500	Old formulation; LD50 > highest dose tested	Anonymous 37 2002c Report 318948 (In DAR 2007)
Bobwhite quail	Quinoclamine	Dietary 5 d	LDD50	394	Input for geomean calculation	Anonymous 38 2001a, 2001b, 2002a Report 318869 (In DAR 2007)
Bobwhite quail	Mogeton 25% WP	Dietary 5 d	LDD50	> 206	Old formulation; LD50 > highest dose tested	Anonymous 39 2001c, 2001d, 2002d Report 318972 (In DAR 2007)
Mallard duck	Quinoclamine	Dietary 5 d	LDD50 LDD50 (extrapol.)	> 686 1107 ª	LD50 > highest dose tested Input for geomean calculation	Anonymous 40 2005 Report 05/896-113TÖ (In DAR 2007)
Japanese quail	Mogeton 50% WG	Dietary 5 d	LDD50 LDD50 (extrapol.)	> 1268 2393 <sup>b</sup>	LD50 > highest dose tested Input for geomean calculation	Anonymous 41 2008 Report 07/586-113FÜ
Birds geomean LDD50 (n = 3)	Quinoclamine Mogeton 50 %WG	Dietary 5d	LDD50	1014 <sup>c</sup>	Acute risk assessment endpoint (birds geomean)	Derived based on lowest reliable LDD50 for bobwhite quail and extrapolated LDD50 for two other species
Bobwhite quail	Quinoclamine	Reproduction 22 weeks	NOAEL EC10	<b>36.2</b> ♀ 37.6 ♂ 35.4	Chronic risk assessment endpoint (NOAEL is preferred, EC10 is considered to be very uncertain since no confidence limits are available)	Anonymous 42 2002b Report 318915 (In DAR 2007)

Table 2.9.1.1-1. Available data on avian toxicity of Quinoclamine, with toxicity data used for risk assessment marked in bold.

a) Calculated according to EFSA 2009/1438, chapter 2.1.2 based on 5 test animals per dose and no mortality.

b) Calculated according to EFSA 2009/1438, chapter 2.1.2 based on 10 test animals per dose and no mortality.

c) Geomean LDD50 calculated according to EFSA 2009/1438, chapter 2.4.1.

Based on three avian species a geometric mean  $LDD_{50}$  (1014 mg a.s./kg bw/d) has been calculated and was proposed for the risk assessment by the applicant. This approach was tentatively accepted by the RMS. However, it may need to be further discussed whether the resulting geomean  $LDD_{50}$  in this case is sufficiently robust, since extrapolated LDD50 values for two of the species were used as input for the calculation. It should be noted that the extrapolation method referred to (as proposed in EFSA 2009/1438) is not always protective it since assumes "*a* 50% binominal probability bound that mortality could have occurred but had simply been missed by chance in the test". Moreover, the mixing of active substance data and formulation data may be an additional source of uncertainty of the calculated geomean value. Member States are asked to provide their views on this issue during the peer review.

# 2.9.1.2. Mammals

An overall summary of the available data on mammalian toxicity of Quinoclamine is given in section 2.6 of this volume. More detailed information on study design and observed effects is available in Volume 3, Annex B.6.

Endpoints relevant for the acute risk assessment on wild mammals are presented in the table below. For the acute risk assessment, the RMS suggests that the previously EU-agreed LD50 of 500 mg a.s./kg b.w. from the study by Ruddock (2002) should be maintained. It is noted that in this study the female mortality was higher than the mortality of males. However, based on a statistical re-evaluation of the dataset the difference between sexes was less than 25% (Von den Berg 2017, reported in Volume 3, Annex B.9 on the active substance, section B.9.1.2.1). Hence, the combined LD50 of 500 mg a.s./kg b.w. was accepted.

Species	Test substance	Time scale	Endpoint	Toxicity (mg a.s./kg	Remarks	Reference
				<b>b.w.</b> )		
Rat	Quinoclamine	Acute oral,	LD50	<b>500</b> ♀♂	Previously EU-agreed	Anonymous 3 2002
		single dose			endpoint for risk	Report 619/141-D6144
		-		200-500 ♀	assessment	(In DAR 2007)
				>500 ♂		
Rat	Quinoclamine	Acute oral,	$\bigcirc$ LD50	300-2000	Only females tested; 5	Anonymous 4 2016
		single dose			animals exposed to	Report G427 /154-768
		-			300 and 1 animal to	-
					2000 mg/kg	
Rat	Mogeton	Acute oral,	⊈∂ LD50	> 1255		Anonymous 12 1998
	50% WG	single dose				Report 619/007

Table 2.9.1.2-1. Available data on acute oral toxicity of Quinoclamine to mammals.

The selection of endpoint for the reproductive risk assessment for wild mammals was discussed during the previous peer review, and the agreed NOAEL was 17.5 mg/kg bw per day (EFSA conclusion 2007). For the purpose pf renewal, the applicant provided an overview of the previous discussions, and the rationale for the agreed value. However, since new guidance has been developed (EFSA 2009/1438) and based on considerations for other compounds following the previous evaluation, there is a need for re-consideration of the selection of endpoint for this assessment. An overview of the available data relevant for the long-term risk assessment to mammals is given in the table below.

|--|

Method, guideline,	Test substance,	Results	Reference
deviations if any,	dose levels	- NOAEL/LOAEL (for sexual function and fertility,	
species, strain, sex,	duration of	parents)	
no/group	exposure	- target tissue/organ	
		- critical effects at the LOAEL (bold text)	
Two generation	Quinoclamine	1 ppm:	RAR Vol. 3,
reproduction study	Purity: 98.5%	Parental:	B.6.6.1/01
		-clinical signs (hunched posture F0/F1)	
In-house method	0, 1, 25, 500 ppm	↓ bw (P1 M: 3%; P2 M: 7%; P2 F 4%)	Anonymous 19
Rat	Corresponding to:	↓ bw gain (P1 M: 4%, P2 M: 11%; P2 F: 4%)	Report 854-111
	F0: 0, 0.07, 1.6,		
Sprague-Dawley	30.9 mg/kg	Offspring:	

	ſ	[	[
Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL (bold text)	Reference
M, F	bw/day in males; 0, 0.08, 1.9 and 37.7 mg/kg	-increased incidence of grey cysts in the lung in F2b offspring reared for 3 months (18 compared to 11 in control group)	
25/sex/group	bw/day in females	25 ppm:	
GLP: No	F1: 0, 0.07, 1.7 and 37.0 mg/kg	Parental: -clinical signs (hunched posture F0/F1)	
	bw/day in males; 0, 0.08, 2.0 and	↓ bw (P1 M: 1%; P2 M: 7%; P2 F 5%)	
	43.8 mg/kg bw/day in	$\downarrow$ bw gain (P1 M: 2%, P2 M: 11%; P2 F: 6%)	
	females	Offspring: -increased incidence of grey cysts in the lung in F2b	
	both generations		
	appropriate diets	S00 ppm: Parental:	
	for at least nine weeks and then	-clinical signs (F0/F1; hunched posture F0/F1) $\downarrow$ <b>bw</b> (P1 M; 4%; P2 M; 10%; P2 F 10%)	
	subjected to two subsequent	↓ <b>bw gain</b> (P1 M: 7%, P2 M: <b>11%</b> ; P2 F: 9%)	
	mating trials. Fresh diets were	$\downarrow$ litter size in F2a and F2b generations	
	prepared and presented weekly	Offspring:	
	to the rats of all generations from	$\downarrow$ <b>bw</b> during lactation (F1a: 13% (m) and 7% (f); F1b:	
	initiation (P1) or weaning (F1b—	14% (m) and 9% (f); F2a: 8% (m) and 9% (f); F2b: 11% (m) and 5% (f)	
	>F2, F2b)	-increased incidence of grey cysts in the lung in F2b offspring	
		NOAEL parental and pups: 25 ppm (1.6 mg/kg bw/day) NOAEL reproductive toxicity: 500 ppm (37 mg/kg bw/day)	
Teratology range finding study	Quinoclamine Purity: 98.1%	Maternal effects: 8 mg/kg bw/day:	RAR Vol. 3, B.6.6.2.1/01
No guideline claimed	0. 8. 50. 80. 200.	No treatment-related effects	Anonymous 33
in study	500 mg/kg	50 mg/kg bw/day:	1986; Anonymous 33 1989
Rat	Vehicle: 0.25%	80 mg/kg bw/day:	(addendum)
Crl:CD (SD) BR	gum tragacanth	-clinical signs (stained urine, stained fur around head) - bw loss/ bw gain (day 7-10: -3.5 g), day 10-13:14%	Report AKJ/2/86; Report AKJ/2A/89
F	Gestation Days 7- 17	(n.s)) ↓FC	(addendum)
5/group		200 mg/kg hw/day.	
GLP: Yes		-mortality (one animal died, two animals were killed in extremis)	
		-clinical signs (lethargy, hunched posture, piloerection,	
		vagina, head)	
		- <b>DW 1058</b> / $\downarrow$ <b>DW gain</b> (day 7-10: -19.8 g, day 10-13: -1.5 g, day 13-17: 42% (n.s.)) $\downarrow$ FC	
		-macroscopic changes (enlarged spleen)	

Method, guideline, does levels         Test substance, does levels         Results         Reference           does levels         POACELLOAEL (or sexual function and fertility, parents)         Interface         Interface           species, strain, sex, process, strain, sex, process, strain, sex, process, strain, sex, process, strain, sex, process, strain, sex, process, strained for an intra- sectical effects at the LOAEL (hold text)         Interface           Sub arrow of the strain section of the strain and died, the remaining four animals were killed in extremis on days 10 or 11 of programscy) edimical signs (charage, bunched posture, piloerection, stained urine, soft stained facess, stained far around anus, vagian, head)         Interface           - bw bess (34 g, dwy 7-10) JFC         JFC         -macroscopic charages (enlarged spleen and adrenals, erosion of the stomach mucosa)           Developmental effects:         200 mg/s (hw/day: jmean foetal weight (27%)         Developmental effects: 200 mg/s (hw/day: jmean foetal weight (27%)           Study is a range finding study only. Date to low number of azimals used in the its and considered appropriate to establish a NADELLOAEL         RAR Vol. 3, B5.6.2.1/02           Teratology study No guideline claimed in study         Quinoclaimic Processopic charges (nalarge spleen, one dam)         RAR Vol. 3, B5.6.2.1/02           Teratology study No guideline claimed in study         Quinoclaimic Processopic charges (enlarged spleen, one dam)         B6.6.2.1/02           Teratology study Rat         Quinoclaimic Processopic charges (enlarged spleen		r	r	r
devisions if any, protes, strain, sposer       does levels duration coposer       -NOAEL/LOAEL (for sexual function and fertility, exposer         - urget tissuorgan       - urget tissuorgan         <	Method, guideline,	Test substance,	Results	Reference
species, strain, sex, no/group       duration of exposure       parents) - critical effects at the LOAEL (bold text)         in protimplantation loss (24.5% compared to 2.4% in controls)       i port-implantation loss (24.5% compared to 2.4% in controls)         S00 marks bwidty:	deviations if any,	dose levels	- NOAEL/LOAEL (for sexual function and fertility,	
Integroup       exposure       - target insued/organ         - infige of the insued organ       - infige affects at the LOAEL (bold text)         1       post-implantation loss (24.5% compared to 2.4% in controls)         S00 mg/kg bw/day:	species, strain, sex.	duration of	parents)	
Amp of up of the second of	no/group	exposure	- target tissue/organ	
Teratology study       Quinoclamine         Parity:       9.8.1%         Victor industriation loss (24.5% compared to 2.4% in controls)         S00 mg/kg bw/day:         -mortality (one animal died, the remaining four animals were killed in extremis on days 10 or 11 of pregnancy)         -etitical signs (tehturg), hunched posture, pilorerection, stained urine, soft stained faces, stained, acceleration, stained faces, stained, acceleration, stained faces, stained, acceleration, stained, acceleration, stained faces, stained, acceleration, stained faces, stained, acceleration, acceleration, stained, acceleration, acceleration, acceleration, acceleration, acceleration, acceleration, acceleration, acceleration, acceleratio	no, gi oup	chposure	- critical effects at the LOAFL (bold text)	
Teratology study       Quinoclamine       Post-implantation loss (24.5% compared to 2.4% in controls).         SOO marks bw/day:       -mortality (one animal died, the remaining four animals were kills (in certemis on days 10 or 11 of pregnancy) -dinical signs (lethargy, hunched posture, pilorection, stained faces, stained far around anus, vagina, head)         - bw loss (-34 g, day 7-10)       IFC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)         Developmental effects:         200 mg/kg bw/day;         I mean foctal weight (8% n.s.)         200 mg/kg bw/day;         I mean foctal weight (27%)         Study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish a NOAELLOAEL         Maternal effects:         No guideline claimed in study         0, 5, 20 and 75         No treatment related effects:         20 mg/kg bw/day;         rater coscopic changes (enlarged spleen, one dam)         F         Gestation Days7-         F         Gestation Days7-         Torsize by a by/day;         GI,P: Yes         Maternal effects:         20 mg/kg bw/day;         No treatment related effects:         20 mg/kg bw/day;         No treatment related effects:				
Controls)       500 mc/k bw/day: -mortality (one animal died, the remaining four animals were killed in extremis on days 10 or 11 of pregnancy) -elinical signs (charges, trained faces, stained far around anus, vagian, head)       -bw loss (-34 g, day 7-10)  FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       -bw loss (-34 g, day 7-10)  FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       -bw loss (-34 g, day 7-10)  FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       -bw loss (-34 g, day 7-10)  FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       -bw loss (-34 g, day 7-10)  FC         -macroscopic changes (enlarged spleen, and adrenals, erosion of the stomach mucosa)       RAR Vol. 3, Bo 6.6.2.102         Study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish a VOAELLOAEL       RAR Vol. 3, Bo 6.6.2.102         No guideline claimed in study       Quinoclamine 90, 5, 20 and 75       Smg/kg bw/day: No treatment related effects       Anonymous 25 1098/B         Rat       Vehicle: 0.25% gun tragecanth       Smg/kg bw/day: No treatment related effects: 20 mg/kg bw/day: No treatment-related ef			$\uparrow$ <b>post-implantation loss</b> (24.5% compared to 2.4% in	
S00 mg/kg bw/day: -mortality (one animal died, the remaining four animals spine tilled in extension days 10 or 11 of pregnancy) -clinical signs (lethargy, hunched posture, piloercetion, spine durine, soft stained faces, stained fur around anus, vagina, head)- Wo loss (-34 g, day 7-10) JPC -mecroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)Developmental effects: 80 mg/kg bw/day: Imean foctal weight (8% n.s.)200 mg/kg bw/day: Imean foctal weight (8% n.s.)200 mg/kg bw/day: Imean foctal weight (27%)Teratology studyQuinoclamine Purity: 98.1%No guideline claimed in study0. 5, 20 and 75 gg widayRatPartGestation Days 7.FGestation Days 7.1724/groupGLP: YesDevelopmental effects: Smg/kg bw/day: Inceanforetal weight (7%)75 mg/kg bw/day: mg/kg bw/day: Interacentie traded effects76 Marka bw/day: Marka bw/day: Interacentie traded effects: Smg/kg bw/day: Interace of aborematilities (innominate artery absent) Tincidence of skeletal variants (skull: hyoid not ossified; vertebray: thoracic centre one or more biblobdod)75 Smg/kg bw/day: Tincidence of skeletal			controls)	
S00 mg/kg bw/day:         - orbital (org. smiral died, the remaining four animals were killed in extremis on days 10 or 11 or pregnancy)         - sinical signs (dehargy, hunched posture, pilorection, stained urine, soft stained faces, stained fur around anus, vagina, head)         - bw loss (-34 g, day 7-10)         1 FC         - macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)         - Developmental effects:         80 mg/kg bw/day:         - postipalantation loss (24.5% compared to 2.4% in controls)         - Imean foctal weight (8% n.s.)         200 mg/kg bw/day:         - postipalantation loss (24.5% compared to 2.4% in controls)         - mean foctal weight (27%)         Study is a range finding study only. Due to low number of animals used in the ti is not considered appropriate to estabilish oNOAELLOAEL         Rat         No guideline claimed         ng/kg bw/day:         ng/kg bw/day:         ng/kg bw/day:         ng/kg bw/day:         ng/kg bw/day:         Pictore         ChCD (SD) BR         guint regacanthere         F       Gestation Days 7-         17       17         14         Vehicle: 0.25%         guint regacanthere         Stang/kg bw/day:				
-mortality (one animal died, the remaining four animals we killed in extremis on days 10 or 11 of pregnancy) -elinical signs (lethargy, hunched posture, piloercetion, stained urine, soft stained faces, stained far around anus, vagina, head) - bw loss (-34 g, day 7-10) [FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach muccos)       -bw loss (-34 g, day 7-10) [FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach muccos)       -bw loss (-34 g, day 7-10) [FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach muccos)       -bw loss (-24, 5% compared to 2.4% in controls) [mean foetal weight (27%)         Teratology study       Quinoclamine       Study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish a VOAELUADLL       RAR Vol. 3, B.6.6.2.1/02         No guideline claimed in study only.       Study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish a VOAELUADLL       B.6.6.2.1/02         No guideline claimed 0, 0, 5, 20 and 75       No treatment related effects       Marenal effects: 100 [Study appropriate to establish a VOAEULOADL]         F       Gestation Days 7.       20 mg/kg bw/day: 100 [Study appropriate]       No macroscopic changes (enlarged spleen, one dam)       Report AKJ/4/86         21/2 group       17       17       17       198       198       198         GLP: Yes       Developmental effects: Smg/kg bw/day: No treatment-rel			500 mg/kg bw/day:	
were killed in extremis on days 10 or 11 of pregnancy) -clinical signs (lethargy, hunched posture, piloerction, stained urine, soft stained faces, stained fur around anus, vagina, head) - bw loss (-34 g, day 7-10) [FC - macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)Developmental effects: 80 mg/kg bw/day; Incean foctal weight (8% n.s.)Developmental effects: 80 mg/kg bw/day; Incean foctal weight (8% n.s.)Teratology study 0 guinoclamine Purity: 98.1%Quinoclamine Purity: 98.1%RAR Vol. 3, B.6.6.2.1/02Teratology study 0 study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish at NOAELLOAEL Study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish at NOAELLOAELRAR Vol. 3, B.6.6.2.1/02Teratology study 0 study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish at NOAELLOAELRAR Vol. 3, B.6.6.2.1/02Teratology study 0 study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish at NOAELLOAELRAR Vol. 3, B.6.6.2.1/02Teratology study 0 study is a range finding study only. Due to low number of animals used in the its not considered appropriate to establish at NOAELLOAELRAR Vol. 3, B.6.6.2.1/02Teratology study 1 is study no treatment related effectsAnonymous 25 1989At 24/group25 1717F 24/groupGestation Days 7 1725 mg/kg bw/day; No reatment-related effects20 mg/kg bw/day; <b< td=""><td></td><td></td><td><b>-mortality</b> (one animal died, the remaining four animals</td><td></td></b<>			<b>-mortality</b> (one animal died, the remaining four animals	
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stained urne, soft stained faces, stained fur around anus, vagina, head)       - bw loss (34 g, day 7-10) [FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       - bw loss (34 g, day 7-10) [FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       - bw loss (34 g, day 7-10) [FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       - bw loss (34 g, day 7-10) [FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       - bw loss (34 g, day 7-10) [FC         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       - bw loss (34 g, day 7-10) [FC         -macroscopic changes (enlarged spleen, one dam)       - bw loss (34 g, day 7-17) [FC         -macroscopic changes (enlarged spleen, one dam)       - bw loss (25 g, day 7-17) [FC         -macroscopic changes (enlarged spleen, 4/24 dams)       - bw login (25% day 7-17) [FC         -macroscopic changes (enlarged spleen, 4/24 dams)       - bw login (25% day 7-17) [FC         -macroscopic changes (enlarged spleen, 4/24 dams)       - bw login (25% day 7-17) [FC         -macroscopic changes (enlarged spleen, 4/24 dams)       - bw login (25% day 7-17) [FC         -macroscopic changes (enlarged spleen, 4/24 dams)       - bw login (25% day 7-17) [FC         -macroscopic changes (enlarged spleen, 4/24 dams)       - bw login (25% day 7-17) [FC         -macroscopic chan			-clinical signs (lethargy, hunched posture, piloerection	
Teratology study       Quinoclamine Purity: 98.1%       Developmental effects: 80 mg/kg bw/day: 1 postimplantation loss (24.5% compared to 2.4% in controls), Jmean foctal weight (8% n.s.)       200 mg/kg bw/day: 1 postimplantation loss (24.5% compared to 2.4% in controls), Jmean foctal weight (27%)         Teratology study       Quinoclamine Purity: 98.1%       Study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish a NOAELLOALL       RAR Vol. 3, B.6.6.2.1/02         Teratology study       Quinoclamine Purity: 98.1%       Study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish a NOAELLOALL       B.6.6.2.1/02         Rat       5 mg/kg bw/day: ng/kg bw/day:       No treatment related effects: 3 mg/kg bw/day: -macroscopic changes (enlarged spleen, one dam)       Report AKJ/4/86         F       Gestation Days 7- 17       17       - FC -macroscopic changes (enlarged spleen, 4/24 dams)       Report AKJ/4/86         GLP: Yes       Developmental effects: 5 mg/kg bw/day: -macroscopic changes (enlarged spleen, 4/24 dams)       -       -         GLP: Yes       Developmental effects: 5 mg/kg bw/day: -macroscopic changes (inlorominate artery absent) fincidence of shelefal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more biolobed)       -         Z0 mg/kg bw/day: -macroscopic cange or more biolobed/biantite; vertebrae: thoracic centre one or more biolobed/biantite;       -			stained uring soft stained faces stained fur around anus	
Vegna, hany       Vegna, hany         Vegna, hany       Witos (34 g, day 7-10)         JPC			vaging head)	
Fit       - 100 task (3-9 g, tay 7-10)         FC       -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)         Developmental effects:       80 mg/kg bw/day;         Imean fortal weight (8% n.s.)       200 mg/kg bw/day;         Imean fortal weight (27%)       Study is a range finding study only. Due to low number of animals used in the it is not considered appropriate to establish a NOAELLONEL.         Teratology study       Quinoclamine Purity: 98.1%         No guideline claimed in study       0, 5, 20 and 75 mg/kg bw/day;         No guideline claimed in study       0, 5, 20 and 75 mg/kg bw/day;         No treatment related effects:       Anonymous 25 1989         Rat       20 mg/kg bw/day;         Pictic: 0.25%       -macroscopic changes (enlarged spleen, one dam)         F       Gestation Days 7-17         17       -100 gain (25% day 7-17)         18       -macroscopic changes (enlarged spleen, 4/24 dams)         GLP: Yes       Developmental effects: 5 mg/kg bw/day: No treatment-related effects         20 mg/kg bw/day: 110cidence of sheelfal variants (skull: hyoid not ossified; vertebrae: thoracic centro one or more biolobed)         75 mg/kg bw/day: 110cidence of sheelfal va			$\operatorname{bw}\log(24 \times \operatorname{dev} 7.10)$	
IPC       -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)         -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)       -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)         Developmental effects:       80 mg/kg bw/day; imean foetal weight (27%)       -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)         Teratology study       Quinoclamine Purity: 98.1%       -macroscopic changes (enlarged spleen and adrenals, erosion of the stomach mucosa)         No guideline claimed in study       Quinoclamine Purity: 98.1%			- Dw 1088 (-54 g, day 7-10)	
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Termson by purity: 98.1%Function effects:Function effects:Function of the field of the fiel	Teratology study	Ouinoclamine	Maternal effects.	RAR Vol 3
No guideline claimed in studyFairly, 50.1%5 mg/kg bw/day: No treatment related effectsDistrict of the state o	Teratology study	Purity: 08 1%	Trater har effects.	B 6 6 2 1/02
No gradenie chained in study       0, 5, 20 and 75 mg/kg bw/day       No treatment related effects       Anonymous 25 1989         Rat       Vehicle: 0.25% gum tragacanth       20 mg/kg bw/day: -macroscopic changes (enlarged spleen, one dam)       Report AKJ/4/86         F       Gestation Days 7- 17       17       - bw gain (25% day 7-17) 1 FC       - bw gain (25% day 7-17) 1 FC       - bw gain (25% day 7-17) 1 FC         24/group       17       Developmental effects: 5 mg/kg bw/day: No treatment-related effects       5 mg/kg bw/day: No treatment-related effects         20 mg/kg bw/day: No treatment-related effects       5 mg/kg bw/day: No treatment-related effects       10 mg/kg bw/day: No treatment-related effects         20 mg/kg bw/day: No treatment-related effects       5 mg/kg bw/day: No treatment-related effects       10 mg/kg bw/day: No treatment-related effects         20 mg/kg bw/day: No treatment-related effects       10 mg/kg bw/day: No treatment-related effects       10 mg/kg bw/day: No treatment-related effects         20 mg/kg bw/day: No treatment-related effects       11 fincidence of skeletal variants (skull: hyoid not ossified; Vertebrae: thoracic centre one or more bilobed)       11 fincidence of skeletal variants (skull: hyoid not ossified; Vertebrae: thoracic centre one or more bilobed/binartite:	No guidalina alaimad	1 unity. 70.170	5 mg/kg hw/daw	<b>D</b> .0.0.2.1/02
In study0, 5, 20 and 73 mg/kg bw/dayNo treatment related effectsAnonymous 23 1989RatVehicle: 0.25% gum tragacanth20 mg/kg bw/day: -macroscopic changes (enlarged spleen, one dam)Report AKJ/4/86FGestation Days 7- 17 $\cdot$ bw gain (25% day 7-17) $\downarrow$ FC -macroscopic changes (enlarged spleen, 4/24 dams)Report AKJ/4/86GLP: YesDevelopmental effects: $5 mg/kg bw/day:$ No treatment-related effectsDevelopmental effects: $5 mg/kg bw/day:$ No treatment-related effects20 mg/kg bw/day: $\cdot$ bw gain (25% day 7-17) $\downarrow$ FC -macroscopic changes (enlarged spleen, 4/24 dams)Holymous 23 (enlarged spleen, 4/24 dams)GLP: YesDevelopmental effects: $5 mg/kg bw/day:$ No treatment-related effects20 mg/kg bw/day: $\uparrow$ incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)75 mg/kg bw/day: $\uparrow$ incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/binartite:	in stude	0 5 20 1 75	<u>5 mg/kg Uw/day.</u>	A
RatIng/kg bw/day1989RatVehicle: 0.25% gum tragacanth20 mg/kg bw/day: -macroscopic changes (enlarged spleen, one dam)Report AKJ/4/86FGestation Days 7- 1775 mg/kg bw/day: - bw gain (25% day 7-17) ↓ FC -macroscopic changes (enlarged spleen, 4/24 dams)Report AKJ/4/86GLP: YesDevelopmental effects: 5 mg/kg bw/day: No treatment-related effectsDevelopmental effects20 mg/kg bw/day: + frc 	in study	0, 5, 20 and 75	No treatment related effects	Anonymous 25
Rat       20 mg/kg bw/day: -macroscopic changes (enlarged spleen, one dam)       Report AKJ/4/86         Crl:CD (SD) BR       gestation Days 7- 17       -bw gain (25% day 7-17) ↓ FC       Report AKJ/4/86         24/group       17       +FC       -macroscopic changes (enlarged spleen, 4/24 dams)         GLP: Yes       Developmental effects: 5 mg/kg bw/day: No treatment-related effects       5 mg/kg bw/day: No treatment-related effects         20 mg/kg bw/day:       ↑incidence of abnormalities (innominate artery absent) ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:		mg/kg bw/day		1989
Crl:CD (SD) BR       Vehicle: 0.25%       -macroscopic changes (enlarged spleen, one dam)       Report AKJ/4/86         F       Gestation Days 7-       75 mg/kg bw/day:       -bw gain (25% day 7-17)       ↓ FC         24/group       17       ↓ FC       -macroscopic changes (enlarged spleen, 4/24 dams)       Imacroscopic changes (enlarged spleen, 4/24 dams)         GLP: Yes       Developmental effects: 5 mg/kg bw/day: No treatment-related effects       5 mg/kg bw/day: No treatment-related effects       Imacroscopic changes (innominate artery absent)         †incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)       75 mg/kg bw/day: 1 fincidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch)         †incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/binartite:	Rat		<u>20 mg/kg bw/day:</u>	
Crl:CD (SD) BRgum tragacanth $75 \text{ mg/kg bw/day:} \\ -bw gain (25% day 7-17) \\ +FC \\ -macroscopic changes (enlarged spleen, 4/24 dams)GLP: YesDevelopmental effects:5 \text{ mg/kg bw/day:} \\ No treatment-related effects20 \text{ mg/kg bw/day:} \\ 1incidence of abnormalities (innominate artery absent) \\ 1incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/)75 \text{ mg/kg bw/day:} \\ 1incidence of abnormalities (innominate artery absent) \\ 1incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch) \\ 1incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:$		Vehicle: 0.25%	-macroscopic changes (enlarged spleen, one dam)	Report AKJ/4/86
FGestation Days 7- 17 $\frac{75 \text{ mg/kg bw/day:}}{\text{-bw gain } (25\% \text{ day } 7-17)}$ $\downarrow$ FC -macroscopic changes (enlarged spleen, 4/24 dams)GLP: YesDevelopmental effects: $5 \text{ mg/kg bw/day:}$ No treatment-related effects $20 \text{ mg/kg bw/day:}$ $\uparrow incidence of abnormalities (innominate artery absent)\uparrow incidence of skeletal variants (skull: hyoid not ossified;vertebrae: thoracic centre one or more bilobed/binartite:$	Crl:CD (SD) BR	gum tragacanth		
FGestation Days 7- 17- bw gain $(25\% day 7-17)$ $\downarrow$ FC -macroscopic changes (enlarged spleen, 4/24 dams)GLP: YesDevelopmental effects: $5 mg/kg bw/day:$ No treatment-related effects $20 mg/kg bw/day:$ $\uparrow incidence of abnormalities (innominate artery absent)\uparrow incidence of skeletal variants (skull: hyoid not ossified;vertebrae: thoracic centre one or more bilobed)75 mg/kg bw/day:\downarrow foetal weight (7%)\uparrow incidence of abnormalities (innominate artery absent,situs inversus, interrupt aortic arch)\uparrow incidence of skeletal variants (skull: hyoid not ossified;vertebrae: thoracic centre one or more bilobed/binartite:$		с с	75 mg/kg bw/day:	
24/group17 $\downarrow$ FC -macroscopic changes (enlarged spleen, 4/24 dams)GLP: YesDevelopmental effects: 5 mg/kg bw/day: No treatment-related effects20 mg/kg bw/day: $\uparrow$ incidence of abnormalities (innominate artery absent) $\uparrow$ incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)75 mg/kg bw/day: $\downarrow$ foetal weight (7%) $\uparrow$ incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)	F	Gestation Days 7-	<b>- bw gain</b> (25% day 7-17)	
24/group       + FC         GLP: Yes       -macroscopic changes (enlarged spleen, 4/24 dams)         Developmental effects:       5 mg/kg bw/day: No treatment-related effects         20 mg/kg bw/day:       ^incidence of abnormalities (innominate artery absent)         ^incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day:         ↓ foetal weight (7%)         ↑ incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic arch)         ↑ incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic arch)         ↑ incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/binartite:		17		
2-rigitup       -macroscopic changes (enlarged spleen, 4/24 dams)         GLP: Yes       Developmental effects:         5 mg/kg bw/day:       No treatment-related effects         20 mg/kg bw/day:       \fincidence of abnormalities (innominate artery absent)         \fincidence of skeletal variants (skull: hyoid not ossified;         vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day:         \footal weight (7%)         \fincidence of skeletal variants (skull: hyoid not ossified;         vertebrae: thoracic centre one or more bilobed,         75 mg/kg bw/day:         \footal weight (7%)         \fincidence of skeletal variants (skull: hyoid not ossified;         vertebrae: thoracic centre one or more bilobed/bipartite:	24/group	17	$\downarrow$ FC	
GLP: Yes       Developmental effects:         5 mg/kg bw/day:       No treatment-related effects         20 mg/kg bw/day:       \frincidence of abnormalities (innominate artery absent)         \frincidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day:         \frincidence of abnormalities (innominate artery absent)         \frincidence of abnormalities (innominate artery absent)         \frincidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch)         \frincidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:	24/group		-macroscopic changes (enlarged spleen, 4/24 dams)	
Developmental effects:         5 mg/kg bw/day:         No treatment-related effects         20 mg/kg bw/day:         ↑incidence of abnormalities (innominate artery absent)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day:         ↓foetal weight (7%)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic arch)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:	CLD: Vac			
Developmental effects:         5 mg/kg bw/day:         No treatment-related effects         20 mg/kg bw/day:         ↑incidence of abnormalities (innominate artery absent)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day:         ↓foetal weight (7%)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: interval approximate artery absent, situs inversus, interrupt aortic arch)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:	GLP: Tes			
5 mg/kg bw/day: No treatment-related effects         20 mg/kg bw/day: ↑incidence of abnormalities (innominate artery absent) ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day: ↓foetal weight (7%) ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch) ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:			Developmental effects:	
No treatment-related effects         20 mg/kg bw/day:         ↑incidence of abnormalities (innominate artery absent)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day:         ↓foetal weight (7%)         ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:			5 mg/kg bw/day:	
20 mg/kg bw/day:         ↑incidence of abnormalities (innominate artery absent)         ↑incidence of skeletal variants (skull: hyoid not ossified;         vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day:         ↓foetal weight (7%)         ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch)         ↑incidence of skeletal variants (skull: hyoid not ossified;         vertebrae: thoracic centre one or more bilobed/bipartite:			No treatment-related effects	
20 mg/kg bw/day:         ↑incidence of abnormalities (innominate artery absent)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day:         ↓foetal weight (7%)         ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:			The doublent folded offolds	
20 Ing/kg bw/day.         ↑incidence of abnormalities (innominate artery absent)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)         75 mg/kg bw/day:         ↓foetal weight (7%)         ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:			20 mg/kg bw/day:	
<pre>incidence of abnormalities (innominate artery absent)  fincidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)  <u>75 mg/kg bw/day:</u>  foetal weight (7%)  fincidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch) fincidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:</pre>			<u>20 mg/kg Uw/uay.</u>	
<pre> incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed)  <u>75 mg/kg bw/day:</u> ↓foetal weight (7%)  ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch)  ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:</pre>			incluence of abnormanues (innominate artery absent)	
vertebrae: thoracic centre one or more bilobed) <u>75 mg/kg bw/day:</u> ↓foetal weight (7%) ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch) ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:			Incidence of skeletal variants (skull: hyoid not ossified;	
<pre>75 mg/kg bw/day: ↓foetal weight (7%) ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch) ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:</pre>			vertebrae: thoracic centre one or more bilobed)	
75 mg/kg bw/day:         ↓foetal weight (7%)         ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch)         ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:				
↓foetal weight (7%) ↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch) ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:			<u>75 mg/kg bw/day:</u>	
↑incidence of abnormalities (innominate artery absent, situs inversus, interrupt aortic arch) ↑incidence of skeletal variants (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:			↓ <b>foetal weight</b> (7%)	
situs inversus, interrupt aortic arch) ↑ <b>incidence of skeletal variants</b> (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:			↑incidence of abnormalities (innominate artery absent,	
↑ <b>incidence of skeletal variants</b> (skull: hyoid not ossified; vertebrae: thoracic centre one or more bilobed/bipartite:			situs inversus, interrupt aortic arch)	
vertebrae: thoracic centre one or more bilobed/bipartite:			<b>†incidence of skeletal variants</b> (skull: hyoid not ossified:	
			vertebrae: thoracic centre one or more bilobed/bipartite:	

			De
Method, guideline,	Test substance,	Results	Reference
deviations if any,	dose levels	- NOAEL/LOAEL (for sexual function and fertility,	
species, strain, sex,	duration of	parents)	
no/group	exposure	- target tissue/organ	
		- critical effects at the LOAEL (bold text)	
		sternebrae: 5 <sup>th</sup> and 6 <sup>th</sup> sternebrae not ossified, one or more	
		bilobed, bipartite or misaligned)	
		NOAEL maternal toxicity: 5 mg/kg bw/day	
		NOAEL developmental toxicity: 5 mg/kg bw/day	
Teratology range	Quinoclamine	Maternal effects:	RAR Vol. 3,
finding study	Purity: 99.0%	10  mg/kg bw/day:	B.6.6.2.1/03
	0 10 50 100	<b>↓bw gain</b> (18%) (Day 6-20)	
No guideline claimed	0, 10, 50, 100		Anonymous 34
in study	mg/kg bw/day	50 mg/kg bw/day:	2002
D .	TT 1 · 1 · 1 · / · /	$\downarrow$ bw gain (27%) (Day 6-20)	D
Rat	Vehicle: 1%	<b>†postimplantation loss</b> (6.2% compared to 2.8% in	Report 619/123-
	aqueous	controls)	D6154
CrI:CD (SD) IGSBR	methylcellulose	↓mean litter weight (2%)	
Б			
F	Gestation Days 6-	$\frac{100 \text{ mg/kg bw/day:}}{100 \text{ mg/kg bw/day:}}$	
7/	19	$\downarrow$ DW gain (41%) (Day 0-20)	
//group		$\downarrow$ gravid uterus weight (1/%)	
CLD. Vez		postimpiantation loss (10.7% compared to 2.8% in	
GLP: Yes		controls)	
		mean litter size (12 compared to 12 6 in control)	
		tinean inter size (12 compared to 12.0 in control)	
		Dovelonmental offects:	
		10 mg/kg bw/day:	
		In the second se	
		-minor foetal variations (filamentous tissue at the top of	
		the tail (two animals))	
		50 mg/kg bw/day:	
		mean foetal weight (11%)	
		-minor foetal variations (filamentous tissue at the top of	
		the tail (one animals))	
		100 mg/kg bw/day:	
		↓mean foetal weight (12%)	
		-minor foetal variations (filamentous tissue at the top of	
		the tail (seven animals))	
		Study is a range finding study only. Due to low number of	
		animals used in the study it is not considered appropriate	
		to establish a NOAEL/LOAEL	
Teratology study	Quinoclamine	Maternal effects:	RAR Vol. 3,
	Purity: 99.0%	5 mg/kg bw/day:	B.6.6.2.1/04
No guideline claimed		No treatment-related effects	
in study	0, 5, 20, 75		Anonymous 26
_	mg/kg bw/day	20 mg/kg bw/day:	2002
Rat	<b>TTTTTTTTTTTTT</b>	-clinical signs (paddling of the forelimbs)	D
	Vehicle: 1%	<b>bw gain</b> (Days 7-8: 62%, Days 17-19: 21%)	Report 619/94-
Crl:CD (SD) IGSBR	aqueous	↓FC	D6154
	methylcellulose	↓mean gravid uterus weight (15%)	
F		↓mean litter weight (13%)	
2.47	Gestation Days 6-		
24/group	19	$\frac{1.5 \text{ mg/kg bw/day:}}{1.5 \text{ mg/kg bw/day:}}$	
CLD V		-clinical signs (paddling of the forelimbs, nose rubbing)	
GLP: Yes		↓ <b>bw gain</b> (Days 17-19: 41%)	

N 4 1 111			<b>D</b> e
Method, guideline,	Test substance,		Reference
deviations if any,	dose levels	- NOAEL/LOAEL (for sexual function and fertility,	
species, strain, sex,	duration of	parents)	
no/group	exposure	- target tissue/organ	
		- critical effects at the LOAEL (bold text)	
		<b>-bw loss</b> (Days 6-7: -4.6 g, Days 7-8: -2.6 g, Days 8-9: -	
		0.4 g)	
		UFC	
		Umean gravid uterus weight (30%)	
		<b>†post-implantation loss</b> (11% compared to 5% in	
		control)	
		[ number of early intrauterine deaths (1.1 compared	
		to 0.7 in control)	
		unean inter weight (29%)	
		14.0 in control)	
		Developmental officers:	
		5 mg/kg bw/day:	
		No treatment-related affects	
		20 mg/kg hw/day.	
		<u>foetal weight (7%)</u>	
		$\uparrow$ skeletal variations (incomplete assification of skull	
		bone and unossified fifth sternebrae)	
		bolie and unossified intersecticorae)	
		75 mg/kg hw/day	
		foetal weight (12%)	
		<b>foetal variations</b> (incomplete ossification of skull bone	
		and unossified fifth sternebrae)	
		<b>malformations</b> (subcutaneous oedema (one animal).	
		retro-oesophageal aortic arch (one foetus), kidney	
		misshapen (one animal). hvdropnephrosis (three animals))	
		······································	
		NOAEL maternal: 5 mg/kg bw/day	
		NOAEL developmental: 5 mg/kg bw/day	
Teratology range	Quinoclamine	Maternal effects:	RAR Vol. 3,
finding study	Purity: 98.1%	<u>8 mg/kg bw/day:</u>	B.6.6.2.1/04
с.		No treatment-related effects	
No guideline claimed	0, 8, 20, 50,		Anonymous 28
in study	80/8 <sup>a</sup> , 200/20 <sup>a</sup> ,	20 mg/kg bw/day:	1986
	500/50 <sup>a</sup>	↑ <b>post-implantation loss</b> (31.1 compared to 8.7 in	
Rabbit		control)	Report AKJ/1/86
New Zealand White	Vehicle: 0.25%		
l_	gum tragacanth	50 mg/kg bw/day:	
F	a	-clinical signs (coloured urine)	
_ /	Gestation Days 6-	↓FC	
5/group	18	<b>post-implantation loss</b> (61.0 compared to 8.7 in	
CLD V		control)	
GLP: Yes			
		$\frac{80/8 \text{ mg/kg bw/day:}}{100000000000000000000000000000000000$	
		-clinical signs (coloured urine)	
		bw (Day 7: 4%, Day 8: 3%, Day 10: 4%)	
		post-implantation loss (25.0 compared to 8.7 in	
		control)	
		200/20 mg/kg bw/day:	
		200/20 mg/kg bw/day: clinical signs (coloured urine)	
		-chinear signs (coloured unite)	
		FC	
		$\uparrow$ <b>nost-implantation loss</b> (30.0 compared to 8.7 in	
		control)	
	I		I

			5
Method, guideline,	Test substance,	Kesults	Keference
deviations if any,	dose levels	- NOAEL/LOAEL (for sexual function and fertility,	
species, strain, sex,	duration of	parents)	
no/group	exposure	- target ussue/organ critical offocts at the LOAFL (hold taxt)	
		- Childen effects at the LOALL (bold text)	
		500/50  mg/kg bw/day	
		<b>-mortality</b> (both animals died, one died on day 9 and the	
		other on day 10 of pregnancy) <sup>b</sup>	
		-clinical signs (lethargy, hunched posture, dark coloured	
		urine)	
		<b>↓bw</b> (Day 8: 12%)	
		↓FC	
		Developmental effects:	
		8 mg/kg bw/day:	
		No treatment related effects	
		20 mg/kg hw/day;	
		20  mg/kg bw/day.	
		control)	
		-malformations (spina bifida (two animals), interrupted	
		aortic arch maior (one animal), hindlimb left malrotated	
		(one animal))	
		50 mg/kg bw/day:	
		$\uparrow$ <b>post-implantation loss</b> (61.0 compared to 8.7 in	
		control)	
		-malformations (interrupted aortic arch major (one	
		animal), kidney left agenesis (one animal))	
		80 mg/kg hw/day:	
		$\frac{00 \text{ mg/kg bw/day.}}{100 \text{ mg/kg bw/day.}}$	
		control)	
		200/20 mg/kg bw/day:	
		↑post-implantation loss (30.0 compared to 8.7 in	
		control)	
		Study is a range finding study only. Due to low number of	
		animals used in the study it is not considered appropriate to astablish a NOAEL/LOAEL	
Teratology study	Quinoclamine	Maternal effects:	RAR Vol 3
Lormorogy brudy	Purity: 98.1%	2.5 mg/kg bw/day:	B.6.6.2.1/04
No guideline claimed	J	No treatment-related effects	
in study	0, 2.5, 7.5, 22.5		Anonymous 27
	mg/kg bw/day	7.5 mg/kg bw/day:	1986
Rabbit		No treatment-related effects	
New Zealand White	Vehicle: 0.25%		Report AKJ/3/86
F	gum tragacanth	<u>22.5 mg/kg bw/day:</u>	
Г	Gestation Dave 6	↓ bw gain (Days 0-28: 5%)	
16/group	18		
10/Broup	10		
GLP: Yes		Developmental effects:	
		<u>2.5 mg/kg bw/day:</u> No treatment related officies	
		7.5 mg/kg bw/day:	
		No treatment-related effects	
		22.5 mg/kg bw/day:	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL (bold text)	Reference
		↓foetal weight (5% n.s.) ↑foetal variations (increased no. of caudal centra ≤15 (84.9% compared to 59.9% in control)) ↑malformations (scoliosis (one animal), spina-bifida (three animals), anomalies of the aortic arch (two animals), sternebral fusions (three animals), hyperextension of limb or paw (one animal))	
		NOAEL maternal toxicity: 22.5 mg/kg bw/day LOAEL maternal toxicity: not established NOAEL developmental toxicity: 7.5 mg/kg bw/day	
Teratology range finding study	Quinoclamine Purity: 99.0%	Maternal effects: <u>5 mg/kg bw/day:</u> No treatment related offects	RAR Vol. 3, B.6.6.2.2/03
No guideline claimed in study	0, 5, 17.5, 30 mg/kg bw/day	<u>17.5 mg/kg bw/day:</u>	Anonymous 35 2002
Rabbit Crl.NZW/Kbl BR	Vehicle: 1% aqueous methylcellulose	↓ <b>bw change</b> (Days 7-28: 12% of controls) ↓FC	Report 619/122- D6154
F 7/group GLP: Yes	methylcellulose Gestation Days 7- 28	30 mg/kg bw/day:         -abortions (two animals, on Day 25 or 29)         ↓ bw change (Days 7-28: 10% of controls)         ↓ FC         ↑ post-implantation loss (22.4% compared to 14.9% in control)         ↑ number of late intrauterine deaths (1.6 compared to 1.0 in control)         ↓ mean litter weight (6%)         ↓ mean foetal weight (3%)         Developmental effects:         5 mg/kg bw/day:         No treatment-related effects         17.5 mg/kg bw/day:         -abortion (one animal Day 24)         30 mg/kg bw/day:         -abortions (two animals, on Day 25 or 29)         ↑ post-implantation loss (22.4% compared to 14.9% in control)         ↑ number of late intrauterine deaths (1.6 compared to 1.0 in control)         ↓ mean litter weight (6%)	
		<b>the mean roetal weight</b> (3%) Study is a range finding study only. Due to low number of animals used in the study it is not considered appropriate to establish a NOAEL/LOAEL	
Teratology study	Quinoclamine Purity: 99.0%	Maternal effects: 5 mg/kg bw/day:	RAR Vol. 3, B.6.6.2.2/04
OECD 414 Rabbit	0, 5, 17.5, 30 mg/kg bw/day	No treatment related effects <u>17.5 mg/kg bw/day</u> ↓ <b>bw change</b> (bw change Days 12-15: 67% of control)	Anonymous 29 2002

Mathad	Tant and a	Describe	Defense
Method, guideline,	1 est substance,		Keierence
deviations if any,	dose levels	- NUALL/LUALL (IOR SEXUAL function and fertility,	
species, strain, sex,	uuration of	parents)	
no/group	exposure	- target ussue/organ oritical officies at the LOAFI (hold text)	
C INTRU/RII DD	V 1 1 1 10/	- critical effects at the LOAEL (bold text)	D (C10/155
Crl.NZW/Kbl BR	Vehicle: 1%	Uniter size (8.4 foetuses per female compared to 9.5 in $(8.4 \text{ foetuses per female compared to 9.5 in})$	Report 619/155-
E	aqueous	control)	D0154
Г	methylcenulose	30 mg/kg hw/day	
24/group	Gestation Days 7-	<u>-mortality (one female killed on Day 18 of gestation<sup>c</sup>)</u>	
24/group	28	hor tanty (one remark kined on Day 18 of gestation )	
GLP Yes	20	bw (Days $4-29$ : 770)	
		LFC	
		<b>post-implantation loss</b> (%/No. of affected dams:	
		24.9/13 compared to 4.8/10 in control)	
		<b>↑early intrauterine deaths</b> (1.0 compared to 0.2 in	
		control)	
		$\uparrow$ <b>late intrauterine deaths</b> (1.4 compared to 0.3 in	
		control)	
		Unter size (7.8 foetuses per female compared to 9.5 in	
		(control)	
		sneeific foetal variations (additional liver lobe cervical	
		remnant of thymus lengthened anterior fontanelle	
		misshapen nasal bone, incomplete ossification of frontal	
		and maxilla bones, slight fusion of sternebrae, abnormal	
		terminal caudal vertebrae and asymmetric ossification of	
		cervical vertebral centra)	
		-malformations (hydronephrosis, 2 animals)	
		Developmental effects:	
		<u>5 mg/kg bw/day:</u>	
		No treatment related effects	
		17.5 mg/kg hu/dev:	
		<b>17.5</b> Ing/kg Dw/day.	
		control)	
		↑ <b>malformations</b> (hydronephrosis, one animal)	
		<u>30 mg/kg bw/day:</u>	
		↑post-implantation loss (%/No. of affected dams:	
		24.9/13 compared to 4.8/10 in control)	
		$\uparrow$ early intrauterine deaths (1.0 compared to 0.2 in	
		control)	
		[late intratterine deaths (1.4 compared to 0.3 in control)	
		<b>litter size</b> (7.8 foetuses per female compared to 9.5 in	
		control)	
		Litter weight (24%)	
		↑ <b>specific foetal variations</b> (additional liver lobe,	
		cervical remnant of thymus, lengthened anterior	
		fontanelle, misshapen nasal bone, incomplete ossification	
		of frontal and maxilla bones, slight fusion of sternebrae,	
		abnormal terminal caudal vertebrae and asymmetric	
		ossification of cervical vertebral centra)	
		- maitormations (hydronephrosis, 2 animals)	
		NOAFL maternal toxicity: 5 mg/kg bw/day	
		NOAEL developmental toxicity: 5 mg/kg bw/day	
		1101111 developmentar toxicity. 5 mg/kg 0w/day	1

The selected endpoint in the previous evaluation (NOAEL 17.5 mg/kg bw per day) was derived from a teratology study on rabbit (Anonymous 29, 2002; 619/155-D6154). At this level, there was a significant but temporary effect on body weight change and a reduction of litter size (8.4 foetuses per female compared to 9.5 in the control, i.e. 12% reduction) that was not considered as adverse at that time. In the next dose level of the rabbit study (30 mg/kg bw per day) there were more adverse effects, such as decreased body weight, more consistent reduction of body weight change, litter size and litter weight. However, the toxicological re-evaluation of this study by the RMS resulted in a proposed NOAEL of 5 mg/kg bw per day. In a corresponding range finding study (Anonymous 35, 2002; 619/122-D6154) similar effects were seen, however, based on re-evaluation by the RMS this was not considered useful for NOAEL setting due to the low number of animals used.

In one teratology study on rat (Anonymous 25, 1989; AKJ/4/86), the toxicological evaluation resulted in maternal and developmental NOAEL of 5 mg/kg bw per day. This is lower than the previously agreed value for rabbit above, but was based on macroscopic changes (enlarged spleen) in one dam at 20 mg/kg bw per day, and was not considered ecotoxicologically relevant at population level. At the next dose, 75 mg/kg bw per day, there was an adverse effect on body weight gain and therefore the ecotoxicologically relevant NOAEL from this study would be 20 mg/kg bw per day. The corresponding range finding study (Anonymous 33, 1986; Anonymous 33, 1989; AKJ/2/86 and AKJ/2A/89) was re-evaluated by the RMS but was not considered useful for NOAEL setting due to the low number of animals used.

A second teratology study on rat (Anonymous 26, 2002; 619/94-D6154) resulted in the same NOAEL of 5 mg/kg bw per day, based on significant effects on body weight gain, mean litter weight (13% reduction), foetal weight (7% reduction) and gravid uterus weight (15% reduction) at 20 mg/kg bw per day that should be considered as ecotoxicologically relevant. The corresponding range finding study (Anonymous 34, 2002; 619/123-D6154) was not considered as useful for NOAEL setting due to the low number of animals used but supported the results from the final study.

A lower NOAEL value, 1.6 mg/kg bw per day, was derived from the two-generation study in rat (Anonymous 19, 1975; 854-111). This value was based on toxicologically adverse effects on body weight and body weight gain in males and females of the second generation at the highest dose level (30.9 mg as/kg bw). It should be noted that statistically significant but smaller effects on body weight and body weight gain were observed also at lower treatment levels, however, were not considered to be adverse by the RMS toxicology expert. In the previous ecotoxicological evaluation, it was considered that the observed effects on body weight gain seen in the *second* generation of the two-generation study on rats were not ecotoxicologically relevant. Therefore, the ecotoxicologically relevant NOAEL from this study was set to the highest dose, 30.9 mg/kg bw per day, which is higher than the relevant NOAEL values from available teratology studies. The relevance of effects in the second generation has however been discussed recently in expert meetings for other compounds, and it was agreed that such effects should not be excluded.

Nevertheless, the RMS proposes that given the large dose spacing in the two-generation study by Anonymous 19 (1975), the NOAEL of 1.6 mg/kg bw per day may be overly protective. Therefore, the NOAEL of 5 mg/kg bw per day from the available teratology studies by Anonymous 25 (1989) and Anonymous 26 (2002) seems reasonable. This may need further discussion. Other MS are asked to provide their views during the peer review.

According to EFSA (2009/1438), supportive information useful for the derivation of ecotoxicologically relevant NOAEL may be derived from short term studies on rodents based on OECD TG 407 and 408. Also corresponding short term data on dog is considered as potentially relevant for the risk assessment since this is an additional species that would therefore reduce uncertainty of the selected endpoint. Available relevant data are listed in the table below. One study on dogs was only accepted for range finding purposes since too few animals were used to give a reliable NOAEL (see toxicology section). More detailed summary and evaluation of the studies is given in Volume 3, Annex B.6. Based on the toxicological evaluation, NOAEL values between 3 and 10 mg/kg bw per day were concluded from these data. This is considered to support that the previously agreed NOAEL (17.5 mg/kg bw per day) may not be protective enough for wild mammals.

Method, guideline,	Test substance,	Results	Reference
deviations if any,	route of	- NOAEL/LOAEL	
species, strain, sex,	exposure, dose	- target tissue/organ	
no/group	levels, duration	- critical effects at the LOAEL (bold text)	
	of exposure		
Oral 28-day study	Quinoclamine	<u>5 ppm:</u>	RAR Vol. 3,
	(purity: 99.0%)	No treatment related effects	B.6.3.1.1/01
OECD TG 407			
	Oral (dietary)	<u>50 ppm:</u>	Anonymous
Rat		No treatment related effects	15 2002
	0, 5, 50, 500,		
Crl:CD <sup>®</sup> (SD)IGSBR	1000 ppm	<u>500 ppm:</u>	Report
		↓ <b>bw gain</b> (M:19%, F:21%, n.s)	619/148
M, F	(corresponding	$\downarrow$ FC (F)	
	to 0, 0.5, 4.7, 44	-changes in haematological parameters, urine analysis parameters,	
5/sex/dose	and 84 mg/kg	organ weights, histopathology in the kidneys	
	bw/day for		
GLP: Yes	males; 0, 0.5,	<u>1000 ppm:</u>	
	5.3, 48 and 90	$\downarrow$ bw gain (M: 42%, F: 41%)	
	mg/kg bw/day	$\downarrow$ FC (M, F)	
	for females)	-changes in haematological parameters, biochemistry, urine analysis	
		parameters, organ weights, macroscopy changes, histopathology in	
	28 consecutive	the kidneys	
	days		
		NOAEL (both sexes): 50 ppm (corresponds to 4.7 (m) and 5.3 (f)	
		mg/kg bw/day)	
		LOAEL (both sexes): 500 ppm (corresponds to 44 (m) and 48 (f)	
0 100 1 ( 1		mg/kg bw/day)	DAD VI 1 2
Oral 28-day study	Quinoclamine	<u>3 mg/Kg bW/day:</u>	RAK VOI. 3,
No. and dollars stated	(purity: 99.0%)	No treatment-related effects	В. 0.3.1.2/01
in study report	Oral	10 mg/kg huy/day	1.000
in study report	(appeulas)	<u>lu inigek g Dw/day:</u> alinical signs (red. or black coloured uring (F))	Anonymous
Deg	(capsules)	-chinical signs (red- of black coloured unite (r))	10 2002 Deport
Dog	0 3 10 30 100	-changes in urinalysis parameters (↑ turbidity (M))	619/1/0
Beagle	$m_{\rm g}/k_{\rm g}$ bw/day		017/147
Deagle	mg/kg Uw/udy	<u>30 mg/kg bw/day:</u>	

Table 2.9.1.2-3. Summary of relevant short-term toxicology studies.

	r	r	F
Method, guideline,	Test substance,	Results	Reference
deviations if any,	route of	- NOAEL/LOAEL	
species, strain, sex,	exposure, dose	- target tissue/organ	
no/group	of exposure	- critical effects at the LOAEL (bold text)	
M, F	28 consecutive	clinical signs (red- or black coloured urine (M, F))	
	days	↓ FC	
1/sex/dose		-changes in urinalysis parameters -organ weight changes	
GLP: Yes		-histopathological changes	
OLI : 105		100 d l (l b	
		$\frac{100 \text{ mg/kg bw/day}^{\circ}}{100 \text{ mg/kg bw/day}^{\circ}}$	
		subdued on Day 3 (F))	
		$\downarrow$ <b>bw loss</b> (Day 4: 13% (M) 18% (F))	
		-poor food consumption (M F)	
		-changes in biochemistry, organ weight, macroscopy.,	
		histopathology	
		Study accepted as a range finding study only. Due to limited	
		nistopathology and low number of animals used it is considered not appropriate to establish a NOAFL/LOAFL	
Oral 90-day study	Ouinoclamine	50 ppm:	RAR Vol. 3.
	(purity not	↓FC (F: 12%)	B.6.3.2.1/01
No guideline stated	stated in study	$\downarrow$ water consumption (15%) (F)	
in study report	report)	-changes in biochemistry	Anonymous
	Oral (diatary)	-organ weight changes	17 1972
Rat	Oral (uletary)	200 ppm:	
	0, 50, 200 and	$\downarrow$ bw gain (M: 6%)	
Sprague-Dawley	1000 ppm	↓FC (F: 11%)	
(SPPF)		↓water consumption (12%) (F)	
МЕ	(equivalent to 0, $\frac{14}{62}$ mg/kg	-changes in biochemistry, organ weight, , histopathology	
IVI, F	5, 14, 62 mg/kg	1000 ppm:	
5/sex/dose	and 0, 3, 13, 65	$\downarrow$ bw gain (F: 7%)	
	mg/kg bw day	↓FC (M: 5%, F: 14%)	
GLP: No	in females)	↓water consumption (M: 23%, F: 17%)	
	12	-changes in biochemistry, organ weight, histopathology	
	15 weeks	NOAEL (both sexes): 50 ppm (corresponds to to 3 mg/kg bw/day)	
		LOAFL (both seves): 200 ppm (corresponds to 14 and 13 mg/kg	
		bw/day in male and females, respectively)	
		Stuay considered limited and accepted as supportive data only	
Oral 90-day study	Quinoclamine	50 ppm:	Vol. 3,
, <u>,</u>	(purity: 99%)	-clinical signs (↑fur staining) (M, F)	B.6.3.2.1/02
OECD 408 (1998)		$\downarrow$ <b>bw gain</b> (Start to week 13: F 17%)	
D-t	Oral (dietary)	$\downarrow$ FC (F, n.s.)	Anonymous
Kat Crl·CD (SD)IGSBP	0.50.200 and	nypoactivity and hyperactivity (at start of treatment) (M, F)	18 2003
CII.CD (SD)IOSDK	800 ppm	-changes in organ weights	
M, F			
	(equivalent to 0,	<u>200 ppm:</u>	
10/sex/dose	3.61, 13.89,	-clinical signs (†fur staining) (M, F)	
CI D. Vac	56./4 mg/kg	<b>Dw gain</b> (Start to week 13: F 21%)	
ULF. IES	males, and 0.	try (r) thypoactivity and hyperactivity (at start of treatment) (M. F)	
	4.56, 17.81,	-changes in myelogram data, haematological parameters,	
	74.81 mg/kg	biochemistry, urinalysis, organ weights, histopathology	
	bw/day in		
	temales)	<u>800 ppm:</u>	

Method, guideline, deviations if any,	Test substance, route of	Results - NOAEL/LOAEL	Reference
species, strain, sex,	exposure, dose	- target tissue/organ	
no/group	of exposure	- critical effects at the LOALL (bold text)	
	13 weeks	-clinical signs (↑fur staining) (M, F) ↓ <b>bw gain</b> (M: 20-28%, F: 27-38%) ↓FC (M, F) ↑hypoactivity and hyperactivity (at start of treatment) (M, F) -changes in myelogram data, haematological parameters, biochemistry, organ weights, macroscopy, histopathology	
		NOAEL (F): not established NOAEL (M): 50 ppm (corresponds to 4.56 mg/kg bw/day)	
		LOAEL (F): 50 ppm (corresponds to 4.56 mg/kg bw/day) LOAEL (M): 200 ppm (corresponds to 13.89 mg/kg bw/day)	
Oral 90-day study	Quinoclamine (purity: 99%)	<u>3 mg/kg bw/day:</u> -clinical signs (coloured urine and faeces) (M, F)	Vol. 3, B.6.3.2.2/01
OECD 409 (1998)	(1)		
	Oral (capsules)	<u>10 mg/kg bw/dag:</u>	Anonymous
Dog	0 0 10 100	-clinical signs (coloured urine and faeces) (M, F)	20 2002
Beagle	0, 3, 10  and  30	$\downarrow$ <b>bw gain</b> (F: 12% n.s.)	
ME	mg/kg Dw/day	-changes in haematological parameters organ weights	
141, 1	13 weeks	histopathology	
4/sex/dose			
		<u>30 mg/kg bw/day:</u>	
GLP: Yes		-clinical signs (coloured urine and faeces) (M, F)	
		↓ <b>bw gain</b> (M: 31%, F: 35%) ↓FC (M, F)	
		-changes in haematological parameters, biochemistry, organ weights, macroscopyin spleen, histopathology	
		NOAEL (both sexes): 3 mg/kg bw/day	
		LUALL (Jour sexes): 10 mg/kg bw/day	

## 2.9.1.3 Potential for endocrine disruption in birds and mammals

No specific data on endocrine disruption in birds is available for quinoclamine.

There were some effects on endocrine organs in the standard mammalian toxicity studies. The effects occurred mainly at high dose levels and might thus be due to systemic toxicity. No clear effect pattern was noted in the assessment of available toxicity studies. However, there were some effects noted at lower dose levels which could not be explained by general toxicity but indicate an endocrine activity (loss of estrous cyclic activity and increased relative thyroid weight noted in the 90-day dog study). In addition, increased incidence of post-implantation loss was noted in one rabbit study at a dose level without maternal toxicity. This effect could be considered as a parameter sensitive to but not diagnostic of EATS (estrogen, androgen, thyroid, steroidogenic). Furthermore, open literature data gives some indications of endocrine effects in fish caused by the metabolite phthalic acid.

It could be noted that the potential for endocrine effects have not been fully investigated in available toxicity studies due to limitations in the test guideline available at the time. For example, sperm parameters and oestrus

cycles have not been investigated in the available studies. Nor have gestation length, vaginal opening or preputial separation been determined.

It could also be noted that the assessment to identify structural alerts for hormonal activity using the OECD QSAR Toolbox was restricted to predict estrogen receptor binding affinity. No other pathways such as androgen receptor pathway was not performed.

According to the draft Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (drafted by EFSA and ECHA staff, with support from JRC 7 December 2017) missing information should be clearly reported and may lead to the need to generate additional information. This will need further discussion.

## 2.9.2 Summary of effects on aquatic organisms

# 2.9.2.1. Bioaccumulation [equivalent to section 11.4 of the CLH report template]

The potential for bioaccumulation of Quinoclamine is considered to be low, and no data on bioaccumulation were considered necessary for the evaluation under Regulation 1107/2009 since estimated and experimental log Pow are below the regulatory triggers of 4 (EG 1272/2008) and 3 (EU 283/2013). This was also the case for metabolites formed in soil and water. It should be noted though, that no such exemption exists under CLP, which requires that all information available is presented and compared with the criteria.

## 2.9.2.1.1. Estimated bioaccumulation

No estimated bioaccumulation data are available and is not needed according to Regulation EU 283/2013 since Log Pow for Quinoclamine is <3. This is also the case for the estimated values on the metabolites. Calculated theoretical log Pow (KOWWIN) for Quinoclamine is 1.5 (Anonymous 2004).

Compound	Log Pow			
-	Experimental*	KOWWIN v. 1.68		
Quinoclamine	2.12	1.50		
2-amino-1,4-naphthoquinone (AN)	1.77	1.01		
2-carboxybenzoic acid (CBA; also known as		1.25		
2-carboxybenzaldehyde)	-	1.25		
2-oxalyl-benzoic acid (M10)	-	0.74		
2-amino-oxalyl-benzoic acid (M11)	-	-0.51		
Phthalamic acid (M9)	-	0.28		
Phthalic acid (M6)	0.73	1.07		

\* Experimental database match referred to in Episuite v4.11 report (ref. Hansch, C. et al, 1995)

# 2.9.2.1.2. Measured partition coefficient and bioaccumulation test data

Partition co-efficient n-octanol / water was measured experimentally by an HPLC method and resulted in log Pow = 1.58 at pH 11 (30°C). It was proposed that the effect of pH is not relevant as Quinoclamine has no measurable dissociation constant (Lumsden 1998). No measured data on bioaccumulation are available.

# 2.9.2.2. Acute aquatic hazard

Available data on the acute toxicity of technical and formulated Quinoclamine and metabolites to fish and aquatic invertebrates are summarised in the table below, with toxicity values used for the risk assessment marked in bold.

Table 2.9.2.2-1. Summary of relevant information on acute aquatic toxicity, with toxicity values used for the risk assessment marked in bold.

Species	Test	Time-scale	Endpoint	Toxicity	Remarks	Reference
	substance	(Test type)		(ing a.s./L)		
Acute toxicity to	fish					
Oncorhynchus mykiss Rainbow trout	Quinoclamine	Semi static 96 h OECD 203	LC50	0.044 (48 h measured)	Key study for classification of Quinoclamine	Anonymous 43 1991a Report 912043117 (In DAR 2007)
Oncorhynchus mykiss Rainbow trout	Mogeton 25% WP	Semi-static 96 h OECD 203	LC50	0.12 (mm)		Anonymous 44 1994a Report 80-91-0045- 02-93 (In DAR 2007)
Oncorhynchus mykiss Rainbow trout	Mogeton 50% WG	Semi-static 96 h OECD 203	LC50	0.042 (nom)	First tier toxicity value for risk assessment	Anonymous 45 1998a Report 98001/01- AAOm
Geomean Rainbow trout (n=3)	Quinoclamine Mogeton 50 %WG Mogeton 25%WP	Semi-static 96 h	LC50	0.061	Input for fish geomean calculation	Species-specific geomean LC50 for rainbow trout
Danio rerio Zebra fish	Mogeton 50% WG	Semi-static 96 h OECD 203	LC50	0.740 (gmm)	Input for fish geomean calculation	Anonymous 46 2016a Report AGK-003/4- 32/A
Pimephales promelas Fathead minnow	Mogeton 50% WG	Semi-static 96 h OECD 203	LC50	0.531 (nom)	Input for fish geomean calculation	Anonymous 47 2016b Report AGK-003/4- 32/C
<i>Oryzias latipes</i> Medaka	Mogeton 50% WG	Semi-static 96 h OECD 203	LC50	0.894 (nom)	Input for fish geomean calculation	Anonymous 48 2016c Report AGK-003/4- 32/F

Species	Test	Time-scale	Endpoint	Toxicity	Remarks	Reference
	substance	(Test type)		(mg a.s./L)		
Fish geomean LC50 (n = 4 from 6 tests)	Quinoclamine Mogeton 50 %WG Mogeton 25%WP	Semi-static 96 h	LC50	0.38	Higher tier toxicity value for risk assessment	Derived by calculating species- specific geomean LC50 first for rainbow trout, and then general geomean LC50 for 4 species.
Oncorhynchus mykiss Rainbow trout	Metabolite M6 Phthalic acid	Static 96 h OECD 203	LC50	> 62.3 (gmm)	First tier toxicity value for risk assessment	Anonymous 49 1999 <sup>a</sup> ADAMA Report R- 11304 (In Folpet DAR 2007)
Acute toxicity to	aquatic inverteb	rates				
Daphnia magna	Mogeton 50% WG	Static 48 h OECD 202	EC50	1.03 (nom)	First tier toxicity value for risk assessment	Heintze 1998b Report 98001/01- AADm
Daphnia magna	Metabolite M6 Phthalic acid	Static 48 h OECD 202	EC50	> 100 (nom)	First tier toxicity value for risk assessment	Gries 1999 <sup>a</sup> ADAMA Report R- 11305 (In Folpet DAR 2007)
Daphnia magna	Metabolite M9 Phthalamic acid	Static 48 h OECD 202	EC50	> 100 (nom)	First tier toxicity value for risk assessment	Scheerbaum 2016a <sup>a</sup> ADAMA Report R-36854
Toxicity to algae and aquatic plants						
See Table 2.9.2.3-1 below.						

nom = nominal; ini = initial measured; mm = mean measured (arithm.); gmm = geomean measured a) Data belong to ADAMA Makteshim Ltd

# 2.9.2.2.1. Acute (short-term) toxicity to fish

Considering OECD TG 203 (1992), reliable data on acute toxicity of the active substance or formulations with Quinoclamine are available for four different fish species, whereof Rainbow trout was the most sensitive. There are no indications from the available data that the co-formulants in the products are more toxic or increase the toxicity of Quinoclamine to fish. Hence, the overall lowest LC50 is proposed for the first tier risk assessment. As a higher tier option a geometric mean LC50 for all four species tested was proposed by the applicant, in accordance with the EFSA Aquatic Guidance Document (2013), chapter 2.1.4.1. Since the available data indicate a comparable toxicity of the active substance and the formulation, this approach was tentatively accepted by the RMS. Other MS are invited to express their views on the approach during the peer review.

One valid study testing the acute toxicity of Metabolite M6 (Phthalic acid) to fish is also available, indicating low toxicity of this metabolite compared to the active substance.

## 2.9.2.2.2. Acute (short-term) toxicity to aquatic invertebrates

# Considering OECD TG 202 (2004), there are no reliable data on acute toxicity of the active substance to

*Daphnia magna*. In the available study with the active ingredient, analytical measurements were conducted only on test solutions before the test initiation, and it is not possible to know if the test concentration decreased over time. Further, no analytical measurements to prove absence of contamination of the control were conducted. According to OECD TG 202 (2004), analytical measurements should also be carried out at the end of the test to ensure stable test concentrations. It is therefore likely that the reported effect values underestimated the toxicity of the test substance.

Reliable acute toxicity data on the representative formulation are available, though, and will preliminarily be used in the risk assessment for Quinoclamine.

Reliable data are also available for Metabolite M6 (Phthalic acid) and Metabolite M9 (Phthalamic acid), showing low acute toxicity for these metabolites to *Daphnia magna*, compared to Quinoclamine.

# **2.9.2.2.3.** Acute (short-term) toxicity to algae or aquatic plants

All available data are listed in Table 2.9.2.3-1 below.

## 2.9.2.2.4. Acute (short-term) toxicity to other aquatic organisms

No further data are available.

## 2.9.2.3. Long-term aquatic hazard

Available data on the chronic toxicity of technical and formulated Quinoclamine and metabolites to fish, aquatic invertebrates, algae and macrophytes are summarised in the table below, with toxicity values selected for the risk assessment marked in bold.

Table 2.9.2.3-1. Summary of relevant information on chronic aquatic toxicity, with toxicity values selected for the risk assessment marked in **bold**.

Species	Test substance	Time-scale (Test type)	Endpoint	Toxicity (mg a.s./L)	Remarks	Reference		
Long-term and chronic toxicity to fish								
Oncorhynchus mykiss Rainbow trout	Quinoclamine	ELS 90 d Flow- through OECD 210	NOEC EC10	<b>0.00213 (nom)</b> 0.0024 (nom)	First tier toxicity value for risk assessment Key study for the classification of Quinoclamine	Anonymous 50 2015 Report AGK- 001/4-43/E		
Oncorhynchus mykiss Rainbow trout	Mogeton 50 % WG	ELS 90 d Pulse exposure OECD 210	NOEC EC10	<b>0.020 (nom)</b> <sup>a</sup> 0.023 (nom)	Higher tier toxicity value for risk assessment.	Anonymous 51 2016d Report AGK- 003/4-43/E		

Species	Test	Time-scale	Endpoint	Toxicity	Remarks	Reference
operes	substance	(Test type)	Lindpoint	(mg a.s./L)	Kennar Kö	Reference
					<b>N.B.</b> This kind of refinement is generally not accepted within the Northern Zone.	
Long-term and	l chronic toxicity	to aquatic inve	ertebrates			
Daphnia	Mogeton 50%	21 d	NOEC /	0.0102 (nom)	Higher tier	Renner 2016
magna	WĞ	Pulse exposure OECD 211	EC10		toxicity value for risk assessment	Report 15 10 48 084W
					<b>N.B.</b> This kind of refinement is generally not accepted within the Northern Zone.	
Chironomus riparius	Quinoclamine	24 d Water- sediment (spiked water) OECD draft	Emergence <sup>b</sup> NOEC(aq) EC10(aq)	0.063 (nom) 0.052 (nom)	First tier toxicity value for risk assessment Key study for the classification	Kleiner 2000a Report 991048113 (In DAR 2007)
Chimmen	Matabalita ANI	GD 1998	Development		of Quinoclamine	Transland and
Chironomus riparius	Metabolite AN 2-Amino-1,4- naphtoquinone	21 d Water- sediment (spiked water) OECD 219	Development NOEC(aq) EC10(aq) Emergence NOEC(aq) EC10(aq)	< 0.145 (ini) <b>0.0813 (ini)</b> 0.674 (ini) 0.643 (ini)	First tier toxicity value for risk assessment	Juckeland 2009 Report 09 10 48 004W
Toxicity to alg	ae					
Scenedesmus subspicatus	Mogeton 50% WG	72 h Static OECD 201	NOEC LOEC EC10 <b>ErC50</b> EbC50	- 0.014 (gmm) - <b>0.029 (gmm)</b> 0.014 (gmm)	First tier toxicity value for risk assessment No NOEC or EC10 based on geomean conc. can be derived from the study	Dengler 1998 Report 98001/01- AASs
Navicula pelliculosa	Quinoclamine	72 h Static OECD 201	NOEC ErC10 ErC50 EbC10 EbC50	0.07 (72-h meas.) 0.115 (72-h meas.) 0.468 (72-h meas.) 0.06 (72-h meas.) 0.185 (72-h meas.)	Poorly reliable but supportive	Barth 2000 Report 991048121 (In DAR 2007)
Pseudo- kirchneriella subcapitata	Metabolite M6 Phthalic acid	72 h Static OECD 201	NOEC ErC10 ErC50 EyC10 EyC50	26.8 (ini) 48.4 (ini) 56.8 (ini) 43.3 (ini) 49.3 (ini)	First tier toxicity value for risk assessment	Scheerbaum 2016b <sup>c</sup> ADAMA Report R- 36849
Pseudo- kirchneriella subcapitata	Metabolite M9 Phthalamic acid	72 h Static OECD 201	pH adjusted: NOEC ErC10 ErC50 EyC10 EyC50	100 (nom) >100 (nom) >100 (nom) >100 (nom) >100 (nom)	First tier toxicity value for risk assessment	Scheerbaum 2016c ° ADAMA Report R- 36850
Toxicity to ma	crophytes					

Species	Test	Time-scale	Endpoint	Toxicity	Remarks	Reference
~F	substance	(Test type)	<b>F</b>	(mg a.s./L)		
Lemna minor	Quinoclamine	7 d	NOEC	0.04 (gmm)		Kleiner 2000b
		Semi-static	ErC10	0.05 (gmm)		Report
		OECD draft	ErC50	0.11 (gmm)		991048122
		1997	EyC10	0.03 (gmm)		(In DAR
			EyC50	0.09 (gmm)		2007)
Myriophyllum	Quinoclamine	14 d	NOEC	0.0086 (gmm)	First tier toxicity	Juckeland
spicatum		Semi-static	ErC10	0.0108 (gmm)	value for risk	2015
		OECD draft	ErC50	0.1347 (gmm)	assessment	Report 14 10
		2013	EyC10	0.0018 (gmm)		48 008 W
			EyC50	0.0613 (gmm)	Key study for	
			Root number		the classification	
			EC10	0.0044 (gmm)	of Quinoclamine	
			EC50	0.0515 (gmm)		
Lemna minor	Mogeton 50%	7 d	NOEC	Not determined		Juckeland
	WG	Semi-static		(<0.05)		2008
		OECD TG	ErC10	0.0453 (nom)		Report 08 10
		221	ErC50	0.116 (nom)		48 013 W
			EyC10	0.0309 (nom)		
			EyC50	0.0711 (nom)		

nom = nominal; ini = initial measured; mm = mean measured (arithm.); gmm = geomean measured a) NOEC is proposed by RMS based on 15% (non-significant) effects on post-hatch survival 90 dpf. The available EC10 value is considered to be uncertain due to the absence of confidence limits. It should be noted that there is no clear evidence as to whether the most sensitive life-stage was exposed during the test. b) No effects on development rate were observed in this study.

c) Data belong to ADAMA Makteshim Ltd

#### 2.9.2.3.1. Chronic toxicity to fish

Considering OECD TG 210 (2013), one reliable chronic study on rainbow trout with the active substance is available, from which a valid endpoint for the risk assessment to fish is derived.

In addition, a higher tier chronic study on rainbow trout was submitted by the applicant, where pulse exposure of the representative formulation was tested in order to simulate more realistic conditions. The study as such was considered to be well performed. However, it should be noted that the proposed refinement based on high-resolution analysis of FOCUS surface water peaks is not accepted within the Northern Zone. Further, there is no clear evidence that the exposure phase covered the most sensitive life stage of the fish. This is further discussed in Vol. 3 CP, section B.9.4.

No chronic toxicity data for fish are available for the metabolites of Quinoclamine.

#### 2.9.2.3.2. Chronic toxicity to aquatic invertebrates

#### Crustaceans

*Considering OECD TG 211 (2012), there are no reliable data on chronic toxicity of the active substance or any of its metabolites to Daphnia magna.* The available study was accepted in the previous evaluation, but is no longer considered to be valid. The validity criterion of at least 60 living offspring per surviving parent in the control (OECD TG 211, revised 2012) was not fulfilled (actual mean value 46.78 offspring/adult). This might

have been an effect of group exposure, which was accepted by the guideline from 1984, available when the study was conducted. According to the current guideline (and since 1998), it is recommended that parent daphnids are held individually during the reproduction test.

Analytical measurements were conducted for the three highest concentrations, although it is recommended in OECD TG 211 (2012) that analytical measurements should be conducted for at least the lowest and highest concentrations. The measured concentration in the second highest treatment was lower than 80% of the nominal concentration, hence it could have been more suitable to express effect values as measured concentrations rather than nominal values. This is however not possible for the NOEC or  $EC_{10}$ , since no analytical measurements are available at these test concentrations. It was further noted that the proposed  $LC_{50}$  value for survival was extrapolated outside the range of tested concentrations in the study. This is normally not recommended (OECD No. 54; guidance on statistical analysis).

For the representative formulation, a higher tier study with *Daphnia magna* is available, where pulse exposure of the representative formulation was tested in order to simulate more realistic conditions. The study as such was considered to be well performed. However, it should be noted that the proposed refinement based on high-resolution analysis of FOCUS surface water peaks is not accepted within the Northern Zone. This is further discussed in Vol. 3 CP, section B.9.4.

## Sediment dwelling organisms

The applicant submitted two chronic water-sediment studies, one with Quinoclamine and one with Metabolite AN (2-Amino-1,4-naphtoquinone), on the sediment-dwelling midge *Chironomus riparius*. Both studies were assessed as valid according to OECD TG 219 (2004). Based on the study results, the metabolite AN appeared to be slightly less toxic than the active substance to *Chironomus*. In addition to the available aquatic (mg/L) endpoints from the studies, the applicant also proposed calculated sediment (mg/kg sed.) endpoints which were extrapolated from the aquatic toxicity endpoints. However, considering the test design (water spiked system), and the limited available data on actual concentrations in the sediment phase, the RMS found it less appropriate to estimate any toxicity endpoints for the sediment phase at all from these studies. The RMS therefore proposes that only the aquatic toxicity endpoints from the overlaying water should be used.

## 2.9.2.3.3. Chronic toxicity to algae or aquatic plants

## <u>Algae</u>

*Considering OECD TG 201 (2006), there are no reliable data available on toxicity of the active substance to green algae.* Hence, for the time being, the risk assessment will rely on the available data on green algae for the representative formulation.

Since Quinoclamine has an herbicidal mode of action, an additional algal species (the diatom *Navicula pelliculosa*) has been tested with the active substance. The available data are not considered valid for risk

assessment, but may be useful as supportive information to conclude on the relatively low toxicity of Quinoclamine to *Navicula pelliculosa* compared to green algae.

Further, two reliable metabolite studies are available, which demonstrate low toxicity of both Metabolite M6 (Phthalic acid) and Metabolite M9 (Phthalamic acid) to green algae, compared to the toxicity of Quinoclamine.

## Macrophytes

Considering OECD TG 221 (2006), reliable data on toxicity to *Lemna gibba* are available both for the active susbtance and for the representative formulation. Considering OECD TG 238 (2014), also a valid sediment-free *Myriophyllum spicatum* toxicity test with the active substance is available.

There are no indications from the available data that the co-formulants in the product are more toxic or increase the toxicity of Quinoclamine to aquatic macrophytes.

## 2.9.2.3.4. Chronic toxicity to other aquatic organisms

No further data are available.

## 2.9.2.4. Comparison with the CLP criteria

#### 2.9.2.4.1. Acute aquatic hazard

All available acute toxicity data are presented above in Table 2.9.2.2-1 (fish and aquatic invertebrates) and Table 2.9.2.3-1 (algae and macrophytes). A summary of the key data is given below.

Acute toxicity to fish: 96 h LC50 = 0.044 mg a.s./L Chronic toxicity to fish: 90 d ELS NOEC = 0.00212 mg a.s./L Acute toxicity to aquatic invertebrates (*Daphnia magna*): 48 h EC50 = 1.03 mg a.s./L Chronic toxicity to aquatic invertebrates (Chironomus sp.): 24 d EC10 = 0.052 mg a.s./L Toxicity to algae: 72 h ErC50 = 0.029 mg a.s./L Toxicity to aquatic macrophytes: 7 d ErC50 = 0.11 mg a.s./L

The toxicity of Quinoclamine to algae (ErC50 = 0.029, the most sensitive group) fulfils the classification criterion of  $\leq 1 \text{ mg/L}$  for Category Acute 1 according to Regulation (EG) 1272/2008.

The proposed M-factor is 10 (appropriate for acute toxicity values within in the range 0.01 - 0.1 mg/L).

# 2.9.2.4.2. Long-term aquatic hazard (including bioaccumulation potential and degradation)

All available chronic toxicity data are presented above in Table 2.9.2.3-1.

Quinoclamine is not rapidly degradable (see section 2.8.2). The substance was not readily biodegradable in 28-day test for ready biodegradability. The primary degradation products cannot be demonstrated to not require classification and therefore primary degradation cannot be used to conclude the substance is rapidly degradable. In a surface water simulation test half-lives were longer than 16 days and ultimate degradation did not reach >70% within 28 days. In two studies on biodegradation in water/sediments half-lives for primary degradation in the total systems were shorter than 16 days but ultimate degradation did not reach >70% within 28 days in the systems. Quinoclamine is considered as hydrolytically stable at environmentally realistic temperatures and pH values. Two studies on aquatic photolysis indicated that under favourable conditions half-lives for primary degradation may be shorter than 16 days but ultimate degradation did not reach >70% within 28 days.

Considering that Quinoclamine is not rapidly degradable in the aquatic environment (see section 2.8.2), the long-term toxicity of Quinoclamine at all taxonomic levels fulfils the classification criterion of  $\leq 0.1$  mg/L for Category Chronic 1 according to Regulation (EG) 1272/2008. The lowest available chronic toxicity value for Quionoclamine is derived from a fish study (NOEC = 0.00213 mg/L). The proposed M-factor is 10 (appropriate for chronic toxicity values within in the range 0.001 – 0.01 mg/L).

When based on the Log Kow, the substance has a 'low potential for bioaccumulation'. Quinoclamine is not expected to bioaccumulate.

## 2.9.2.5. Conclusion on classification and labelling for environmental hazards

Quinoclamine shall be classified as

- a) Acute (short-term) aquatic hazard Category Acute 1, M-factor = 10
- b) Long-term aquatic hazardCategory Chronic 1, M-factor = 10

## 2.9.2.6. Assessment in relation to the B and T criteria (Regulation 1107/2009)

## **B-criterion:**

The potential for bioaccumulation of Quinoclamine and its metabolites formed in soil and water is considered to be low. No data on bioaccumulation are considered necessary since estimated and experimental log Pow are below the regulatory trigger of 3 (EU 283/2013).

# **T-criterion:**

An active substance fulfils the criteria for toxicity in aquatic organisms, as stated in Annex II to Regulation (EC) 1107/2009, if the long-term no-observed effect concentration for marine and freshwater organisms is less than 0.01 mg/L.

Quinoclamine fulfils the T-criterion, with a of NOEC 0.00213 mg a.s./L from the ELS study on rainbow trout (Anonymous 50, 2015).

Based on the available data, none of the metabolites fulfils the T-criterion.

# 2.9.2.7 Potential for endocrine disruption in aquatic organisms

No indications of endocrine disrupting properties of Quinoclamine have been found in the available data set for aquatic organisms. However, no specific studies are available to conclude on potential for endocrine disruption. The open scientific literature presented by the applicant does not provide any indications of endocrine activity of the active substance in fish. Further considerations may be needed in order to conclude the assessment on endocrine disruption in fish.

Regarding metabolites, one published *in vitro* study gives some indications of endocrine effects in fish caused by phthalic acid (Maradonna et al. 2013). Due to uncertainties on the identity of the test substance, the study is considered less reliable but may be supportive if other evidence become available. See Vol. 3 CA, section B.9.2.3 for further information.

## 2.9.3 Summary of effects on arthropods

## 2.9.3.1 Effects on bees

The relevant available data on toxicity to bees are summarised in the table below, with endpoints selected for the risk assessment marked in bold.

Species	Test	Time	Endpoint	Toxicity	Remarks	Reference
	substance	scale				
Apis mellifera L.	Mogeton	48 h	Oral LD <sub>50</sub>	> 401.0 µg a.s./bee	a, b	Franke 2014
(adult honey bee)	50% WG	Acute	Contact LD <sub>50</sub>	> 411.2 µg a.s./bee	a, b	Report 14 10 48
						151 B
Apis mellifera L.	Mogeton	48 h	Oral LD <sub>50</sub>	> 188.1 µg a.s./bee		Barth 2008
(adult honey bee)	50% WG	Acute	Contact LD <sub>50</sub>	$> 200 \ \mu g a.s./bee$		Report 08 10 48
						022 B
Bombus terrestris	Mogeton	96 h	Oral LD <sub>50</sub>	> 287.6 µg a.s./bee	a	Amsel 2015
(adult bumblebee)	50% WG	Acute	Contact LD <sub>50</sub>	> 498.1 µg a.s./bee	а	Report 14 10 48
						057 A
Osmia bicornis L.	Mogeton	96 h	Oral LD <sub>50</sub>	101.1 µg a.s./bee	a	Schnurr 2015
(adult solitary bee)	50% WG	Acute	Contact LD <sub>50</sub>	283.5 µg a.s./bee	а	Report 14 10 48
						154 B
Apis mellifera L.	Mogeton	10 d	LD50	78.3 µg a.s./bee/day	a, b	Ruhland 2015
(adult honey bee)	50% WG	Chronic	LD20	53.5 µg a.s./bee/day		Report 14 10 48
			LD10	43.9 µg a.s./bee/day		153 B
			NOED	49.6 µg a.s./bee/day		
			NOEDhpg	119.2 µg a.s./bee/day	b	
Apis mellifera L.	Mogeton	120 h	LD50	50.9 µg a.s./larva		Kleebaum 2015
(honey bee larvae)	50% WG	Repeated	NOED	19.8 µg a.s./larva	a, b	Report 14 10 48
		exposure				152 B

 Table 2.9.3.1-1. Summary of relevant information on toxicity to bees, with endpoints selected for the risk assessment marked in bold.

a) Endpoint used for the risk assessment performed according to EPPO (2010

b) Endpoint used for the risk assessment performed according to the EFSA (2013)

## 2.9.3.2 Effects on arthropods other than bees

The relevant available data on toxicity to arthropods other than bees are summarised in the tables below, with endpoints selected for the risk assessment marked in bold.

Standard laboratory studies with the old formulation Mogeton 25% WP tested on a range of arthropod species are available from the previous evaluation of Quinoclamine. These studies indicate a low toxicity (< 30% effect) of Quinoclamine to *Aphidius rhopalosiphi, Typhlodromus pyri, Pardosa spp.* and *Poecilus cupreus* when tested at doses comparable to the currently proposed GAP. For *Aleochara bilineata*, one older study with Mogeton 25% WP showed up to 70% effect on reproduction at a relevant dose (Ullrich 1992b), however a newer study performed with Mogeton 50% WG (identical to the representative formulation Mogeton TOP), revealed no effects at a relevant dose (Kühner 1998). Moreover, the older study by Ullrich (1992b) was considered less reliable since no toxic reference was included in the test. Therefore, this study was not used for the risk assessment.
Species	Test substance	End point	Toxicity (kg a.s./ha)	Remarks	Reference		
Indicator species		1	(				
Aphidius rhopalosiphi (parasitic wasp)	Mogeton 25% WP	48-h LR50 and ER50 (fecundity)	> 3.81	< 30 % effect up to 3.81 kg a.s./ha	Kleiner 1999a Report 99 10 48 069 (In DAR 2007)		
<i>Typhlodromus pyri</i> (predatory mite)	Mogeton 25% WP	7-d LR50, 14-d LR50 and ER50 (fecundity)	> 3.81	< 30 % effect up to 3.81 kg a.s./ha	Kleiner 1999b Report 99 10 48 070 (In DAR 2007)		
Additional species	Additional species						
Pardosa spp. (lycosid spider)	Mogeton 25% WP	14-d LR50 and ER50 (feeding capacity)	> 3.81	< 30 % effect up to 3.81 kg a.s./ha	Kleiner 1999c Report 99 10 48 068 (In DAR 2007)		
Poecilus cupreus (carabid beetle)	Mogeton 25% WP	14-d LR50 and ER50 (feeding capacity)	> 3.81	< 30 % effect up to 3.81 kg a.s./ha	Ullrich 1992a Report 1396/30-91 (In DAR 2007)		
Aleochara bilineata (rove beetle)	Mogeton 25% WP	2-month ER50 (reproduction)	< 3.81	70 % effect Study considered as less reliable	Ullrich 1992b Report 1396/20-91 (In DAR 2007)		
Aleochara bilineata (rove beetle)	Mogeton 50% WG	10-week ER50 (reproduction)	> 3.75	< 30 % effect up to 15 kg a.s./ha	Kühner 1998 Report 98001/01- NLAb (In DAR 2007)		

Extended laboratory data are available for the indicator species *Aphidius rhopalosiphi* and *Typhlodromus pyri*, as well as one additional species, *Orius laevigatus*. For *Typhlodromus pyri* significant effects on reproduction were observed at rates  $\geq 0.527$  kg a.s./ha, whereas no significant effects were observed on the other two species tested up to and including at least the double highest recommended application rate for Quinoclamine.

An aged residue study with *Typhlodromus pyri* was also submitted, showing no significant effects on mortality or reproduction after 28 days exposure to aging residues of the test substance when applied at a rate corresponding to the proposed GAP.

Species	Life	Test	Time	End point	Dose	% effect	ER50	Reference
	stage	substance	scale		(kg a s /ba)		(kg as/ba)	
		substrate			a.s./11a)		a.s./11a)	
Extended labor	ratory stud	ies		•				•
Aphidius	Females	Mogeton	14	Mortality,	0.527	< 30% (n.s.)	ER50 >	Sipos 2008a
rhopalosiphi	0-48 h	50% WG	days	repellency,	1.054	at all doses	8.432	Report
(parasitic	old	horloss		repro-	2.108			07/586- 251ED
wasp)		seedlings		duction	8.432			5511-D
Typhlodromus	Proto-	Mogeton	7 days	Mortality	0.0659	< 30% (n.s.)	LR50 >	Sipos
pyri	nymphs	50% WG			- 8.432	at all doses	8.432	2008b
(predatory			14	Repro-	Test 1			Report
mite)		bean leaf	days	duction	0.527	-32.8% *	ER50 >	07/586-
		disks			1.054	-53.3% *	0.527 <sup>a)</sup>	331KA
					2.108	-46.5% *		
					8.432	-87.3% *		
					Test 2			
					0.0659	-13.7% (n.s.)		
					0.132	-18.6% (n.s.)		
					0.264	-18.7% (n.s.)		
					1.054	-23.0% (n.s.)		
Orius	Second	Mogeton	21	Mortality,	1.85	< 30% (n.s.)	ER50 >	Rathke
laevigatus	instar	50% WG	days	repro-	2.73	at all doses	9.25	2016a
(predatory	nymphs			duction	4.11			Report
bug)		bean			6.17			160405DH
Aged residue s	tudies	leaves			9.25			/10E108//
Tunklo duomus	Droto	Mogeter	28	Mortelity	2 955 (ini)	$< 200/(m_{a})$	1.050 \	Dathlea
1 ypnioaromus nvri	nymphs	50% WG	20 days	Mortality	5.855 (111)	< 50% (fl.s.) at all doses	$1 \text{K}_{30} > 3855$	2016b
(predatory	inginipins	20/0 110	aays	Repro-	3.855 (ini)	ut un dobes	ER50 >	Report
mite)		whole		duction	,		3.855	160405DH
		bean			Day 0-14	-45.3% *		/ IRD16877
		plants						
					Day 14-28	7.570( ( )		
					(aged residues)	/.5/% (n.s.)		

\* significant effect

*n.s.* = Not significant effect a) The applicant proposed ER50 = 3.3 kg a.s./ha based on both tests in the study, and excluding results at 0.527 - 1.054 kg a.s./ha). This approach was considered less reliable by the RMS.

## 2.9.4 Summary of effects on non-target soil meso- and macrofauna

## 2.9.4.1 Effects on earthworms

The relevant available data on toxicity to earthworms are summarised in the table below, with endpoints selected for the risk assessment marked in bold.

Species	Test substance	Application method /OM	Time scale	End point	Toxicity (mg a.s./kg soil dw)	Remarks	Reference
Laboratory s	studies						
Eisenia fetida	Quinoclamine	Test item incorporated into the soil / 5% peat	Chronic, 56 days	NOEC EC10 EC25 EC50	6.5 <b>5.1</b> 7.5 11.4	a	Friedrich 2009 Report 09 10 48 067S
Eisenia fetida	Mogeton 50 % WG	Test item incorporated into the soil / 5% peat	Chronic, 56 days	<b>NOEC</b> EC10 EC20 EC50	<b>6.9</b> 12.3 14.8 20.4		Vértesi 2008 Report 07/586- 211G
Eisenia fetida	Metabolite M6 Phthalic acid	Test item incorporated into the soil / 5% peat	Chronic, 56 days	<b>NOEC</b> EC10 EC20 EC50	<b>68.0</b> > 122.4 > 122.4 > 122.4	b	Friedrich 2016a Report 16 10 48 133 S
Eisenia fetida	Metabolite M10 2-(Carboxy- carbonyl) benzoic acid	Test item incorporated into the soil / 5% peat	Chronic, 56 days	<b>NOEC</b> EC10 EC20 EC50	<b>61.2</b> > 61.2 > 61.2 > 61.2 > 61.2	с	Friedrich 2016b Report 16 10 48 134 S
Field studies							
Earthworms	Mogeton 50 % WG	Field study in Germany / Grassland / 5.33% OM / Application in October / Plot sprayer	1 year	NOEC	<b>3.75 kg</b> <b>a.s./ha</b> (not analytically verified)	grassland	Schulz 2011 Report 10 10 48 002 F

 Table 2.9.4.1-1. Summary of relevant information on toxicity to earthworms

a) Given the observed dose response pattern with 17.7% non-significant effect on reproduction at 6.5 mg a.s./kg dw soil, the proposed NOEC at this level seems to be very uncertain. In this case, the RMS considered the EC10 of 5.1 mg a.s./kg dry soil provided by the applicant as more robust than the NOEC.

b) The applicant proposed NOEC = 122.4 mg/kg soil dw, However, the RMS considered that the 18.5% effect on reproduction at this treatment level may be regarded as biologically relevant although not statistically significant. It is not clear how the study author estimated EC10 to be > 122.4 mg/kg soil dw, since no ECx analysis was provided. c) NOEC = highest tested concentration

In addition to the standard laboratory tests, a higher-tier field study with the representative formulation is available. The field study was conducted on grassland and therefore its representativeness for the proposed use of Quinoclamine in nursery stock plants is uncertain. On the other hand, the relevant test guideline explicitly recommends grassland as the preferred study site for testing earthworms in the field, since earthworm density and diversity in grassland are "generally higher and more stable than on arable land which makes it easier to detect significant effects on earthworm populations" (ISO 11268-3 updated by Kula et al. 2006). Hence, considering the community structure of earthworms, the RMS proposes that the available field study results may be considered as suitable also for the risk assessment in nursery stock plants. However, considering the lack of verification of

exposure levels in the soil as well as the less optimal timing of the study, the reliability of these higher-tier data may need further discussion.

## 2.9.4.2 Effects on other soil macro organisms

The relevant available data on toxicity to other soil macro organisms are summarised in the table below, with endpoints selected for the risk assessment marked in bold.

Species	Test	Application	Time	End point	Toxicity	Remarks	Reference
	substance	method /	scale		(mg a.s./kg		
		ОМ			soil dw)		
Laboratory	studies						
Folsomia	Mogeton 50	Test item	Chronic,	NOECmortality	514		Rathke
candida	% WG	incorporated	28 days	NOECreproduction	159		2016c
		into the soil		EC10	3.63	а	Report
		/ 5% peat		EC20	70.4	a	160405DH /
				EC50	n.d.		ICR16877
Folsomia	Metabolite	Test item	Chronic,	NOECmortality	68.0		Friedrich
candida	M6	incorporated	28 days	NOECreproduction	122.4		2016c
	Phthalic acid	into the soil		EC10, EC20, EC50	> 122.4		Report 16 10
		/ 5% peat					48 129 S
Folsomia	Metabolite	Test item	Chronic,	NOEC	61.2		Friedrich
candida	M10	incorporated	28 days	$EC_{10}, EC_{20}, EC_{50}$	> 61.2		2016d
	2-(Carboxy-	into the soil					Report 16 10
	carbonyl)	/ 5% peat					48 130 S
	benzoic acid						
Hypoaspis	Mogeton 50	Test item	Chronic,	NOECmortality	514		Rathke
aculeifer	% WG	incorporated	14 days	NOECreproduction	87.9		2016d
		into the soil		EC10	70.9	а	Report
		75% peat		EC <sub>20</sub>	180 n d	а	160405DH /
II	M-+-h-1:+-	Tratitana	Character	EC50	n.u. 122.4		IHL108//
Hypodspis	Metabolite	incorporated	14 days	NOEC	122.4		Beport 16 10
ucutetjer	Phthalic acid	into the soil	14 days	$EC_{10}, EC_{20}, EC_{50}$	> 122.4		18 131 S
	i initialic aciu	/ 5% peat					40 151 5
Hypoaspis	Metabolite	Test item	Chronic	NOFC	61.2		Schulz 2016b
aculeifer	M10	incorporated	14 days	$FC_{10}$ $FC_{20}$ $FC_{50}$	> 61 2		Report 16 10
ucuicijer	2-(Carboxy-	into the soil	14 days	$LC_{10}, LC_{20}, LC_{30}$	> 01.2		48 132 S
	carbonyl)	/ 5% peat					40 132 5
	benzoic acid	, e ,o peut					
Field studies	5						
Collembola	Mogeton 50	Field study	12.5	NOECabundanaa	3 75 kg	orassland	Henkes and
and	% WG	in Germany	months	TOE Cabundance	3.75 Kg	grassiana	Henkes 2017
Acarina		/ Grassland/	montilis				Report
cumu		3.66% OM /			(2.08 mg		1640054
		Application			a.s./kg soil		
		in May /			dw, initial		
		Boom			measured,		
		sprayer			at 10 cm		
					depth)		

Table 2.9.4.2-1. Summary of relevant information on toxicity to other soil macro organisms

a) Large 95% confidence intervals indicate that the EC10 and EC20 are uncertain

In addition to the standard laboratory tests, a higher-tier field study with the representative formulation is available. The field study was conducted on grassland and therefore its representativeness for the proposed use of Quinoclamine in nursery stock plants is uncertain. However, since the concentrations of test substance in the soil were satisfactorily verified on the day after application in the field, the RMS proposes that the NOEC from the study can be considered in the risk assessment together with the calculated PECsoil, also for nursery stock plants. This reasoning is further evaluated in the risk assessment in Volume 3, Annex B.9 on the representative formulation, section B.9.8.

## 2.9.5 Summary of effects on soil nitrogen transformation

The available data on effects on nitrogen transformation are summarised in the table below.

Tuble 1/10 11 Summur J of Fele funt mormation on effects on mit ogen transformation.						
Measurement	Test	Time scale	No effects (< 25 % difference	Remarks	Reference	
parameter	substance		to control) up to			
Nitrogen	Quinoclamine	28 days	5 mg a.s./kg soil dw		van der Kolk 2002	
transformation		57 days	25 mg a.s./kg soil dw		Report 1052.011.747	
					(In DAR 2007)	

Table 2.9.5-1. Summary of relevant information on effects on nitrogen transformation.

#### 2.9.6 Summary of effects on terrestrial non-target higher plants

The available data on toxicity to terrestrial non-target higher plants are summarised in the table below, with endpoints selected for the risk assessment marked in bold.

Test type	Test substance	Species	Most sensitive species	Toxicity (kg a.s./ha)	Remarks	Reference
Vegetative vigour (n=6)	Quinoclamine	<u>Monocot</u> Avena sativa Zea mays Allium cepa <u>Dicot</u> Trifolium pratense Daucus carota Brassica napus	Brassica napus (rape)	NOEC = 0.435 ER50 ~ 0.87	Previously EU-agreed endpoint	Fiebig 2000 Report 990914SS (TNW71151) (In DAR 2007)
Vegetative vigour (n = 6)	Mogeton 50% WG	<u>Monocot</u> Avena sativa Allium cepa <u>Dicot</u> Brassica napus Daucus carota Cucumis sativus Pisum sativum	Pisum sativum (pea)	ER50≥3.75	Limit test; NOEC could not be determined	Friedrich 2015a Report 15 10 48 002 P
Seedling emergence (n = 6)	Mogeton 50% WG	<u>Monocot</u> Avena sativa Allium cepa <u>Dicot</u> Brassica napus Daucus carota Cucumis sativus Pisum sativum	Allium cepa	ER50≥3.75	Limit test; NOEC could not be determined	Friedrich 2015b Report 15 10 48 001 P

Table 2.9.6-1. Summary of relevant information on effects on terrestrial non-target higher plants.

## 2.9.7 Summary of effects on other terrestrial organisms (flora and fauna)

No further studies on terrestrial organisms are available.

#### 2.9.8 Summary of effects on biological methods for sewage treatment

The available data on effects on sewage treatment are summarised in the table below.

Table 2.9.8-1: Summary	v of relevant information	ation on effects on	biological meth	ods for sewage treatment.
				- · · · · · · · · · · · · · · · · · · ·

Test type/organism	Endpoint	Reference
Activated sludge	3-h EC <sub>50</sub> >180 mg a.s./L	Mattock 2002; Report 619/146-D2149 (In DAR 2007)

#### 2.9.9 Summary of product exposure and risk assessment

#### 2.9.9.1 Summary of product exposure and risk assessment for birds and mammals

A risk assessment for birds and mammals was conducted according to the Guidance Document on Risk Assessment for Birds and Mammals (EFSA 2009/1438).

#### Birds

#### Tier 1

Based on first tier calculations, the acute risk to birds is acceptable in all uses at the lower application rates (1.875 and 1.44 kg a.s./ha). However, at the highest application rate (3.75 kg a.s./ha), unacceptable acute risks were identified both in golf greens and in plant nurseries. Moreover, unacceptable long-term risks were identified in all uses. For the uses on golf greens, concern was mainly raised for large herbivorous birds (acute and long-term risks) and for small insectivorous birds (long-term risks). For the uses in nursery stock plants, concern was raised for small insectivorous birds feeding on foliar arthropods (long-term risks), which is only relevant for the proposed use with tractor mounted downward spraying at 1.44 kg a.s./ha.

#### Higher tier

To address the identified risks to birds, the applicant also submitted a refined risk assessment. Based on this assessment, for the intended uses of Mogeton TOP on golf greens, the RMS proposes that acceptable risk to birds can be concluded, when taking into account all the available higher-tier information and reasoning about low attractiveness of golf greens as foraging habitats for birds.

Regarding the proposed uses in nursery stock plants, acceptable use can be concluded for hand-held application directly to the substrate surface, while concern remains for outdoor tractor mounted downward spraying of plants at 1.44 kg a.s./ha. Following this use, an unacceptable long-term risk to small insectivorous birds feeding on foliar arthropods was identified in the first-tier risk assessment. This risk was not further discussed by the applicant.

#### Mammals

#### Tier 1

Based on first tier calculations, unacceptable acute and long-term risks to mammals were identified in all proposed uses. For the uses on golf greens, concern was mainly raised for large herbivorous mammals, small herbivorous mammals (acute and long-term risks), and small insectivorous mammals (long-term risk). For the uses in nursery stock plants, concern was raised for small herbivorous mammals, small omnivorous mammals (acute and long-term risks), and small herbivorous mammals, small omnivorous mammals (acute and long-term risks), and small herbivorous mammals, small omnivorous mammals (acute and long-term risks), and small insectivorous mammals, small omnivorous mammals (acute and long-term risks), and small insectivorous mammals (long-term risk).

#### Higher tier

To address the identified risks to mammals, the applicant also submitted a refined risk assessment. Based on this assessment, for the intended uses of Mogeton TOP on golf greens, the RMS proposes that acceptable risk to mammals can be concluded, when taking into account all the available higher-tier information and reasoning about low attractiveness of golf greens as foraging habitats for mammals.

Also in nursery stock plants, low attractiveness of the treated area as foraging habitat to most mammals can be assumed based on the available data. However, the wood mouse (*Apodemus sylvaticus*) was identified as a relevant focal species, requiring a refined numerical risk assessment. As some input parameters (including the selected reproductive endpoint) proposed for this refined risk assessment may need further revisions following the peer review of this RAR, no conclusion regarding the risk to small mammals in plant nurseries can be drawn at this stage.

#### 2.9.9.2 Summary of product exposure and risk assessment for aquatic organisms

A risk assessment for aquatic organisms was performed according to the EFSA Aquatic Guidance Document (EFSA 2013/3290).

#### Quinoclamine

#### Tier 1

A first tier risk assessment was performed considering surface water and sediment PEC simulations for the active substance based on FOCUS Steps 3-4, but with some modifications of the standard assumptions in the model which were in general accepted by the RMS (see Volume 3, Annex B.8 on the representative formulation).

*Golf greens:* For hand-held application on golf-greens acceptable aquatic risk was demonstrated at Tier 1 when considering a 20 meter vegetated buffer zone together with 95% spray drift reduction by nozzles. For tractor mounted application, no safe use could be concluded at Tier 1.

*Tree nurseries:* Acceptable risks without mitigation measures could be concluded for all proposed uses in greenhouse and walk-in tunnel. Following outdoor application in tree nurseries, acceptable risk was also

demonstrated at Tier 1 for all relevant FOCUS drainage (D) scenarios (considering a 20 meter vegetated buffer zone together with 95% spray drift reduction by nozzles), but the run-off (R) scenarios were not acceptable.

#### Higher tier

The applicant proposed that a few additional FOCUS scenarios could be demonstrated as acceptable, when considering the available higher tier data (geomean acute fish LC50 and chronic pulse exposure studies for fish and *Daphnia*) together with a visual graphical evaluation of PECsw peaks simulated in FOCUS Step 4 (20 meter vegetated buffer zone together with 95% spray drift reduction by nozzles). The geomean approach for the acute risk assessment was tentatively accepted by the RMS, whereas the pulse exposure approach for the long term risk assessment will need further consideration. Both pulse exposure studies as such were considered to be well performed. However, there is no clear evidence that the most sensitive life stage was exposed during the fish test. Further, it should be noted that the associated refinement based on high-resolution analysis of FOCUS surface water peaks is generally not accepted within the Northern Zone. Other MS are invited to express their views during the peer review.

#### Metabolites

For the relevant metabolites in surface water and sediment, acceptable surface water and sediment PEC simulations were only available based on FOCUS Steps 1-2.

The risk to surface water and sediment organisms from the following relevant photolytic degradation products were assessed at Tier 1: M6 (Phthalic acid), M9 (Phthalamic acid), M10 (2-Oxalyl-benzoic acid), M11 (2-Amino-oxalyl-benzoic acid), 2-Carboxy-benzaldehyde and 'Unknown 2'. None of these degradation products are considered to retain the toxophore of Quinoclamine. Therefore, when toxicity data were lacking the metabolites were assumed to be equally toxic as Quinoclamine. Based on FOCUS Step 2, acceptable risk from the metabolites M9, M10 and M11 could be concluded for all uses (except for metabolite M11 in plant nurseries in southern Europe at the highest application rate of 3.75 kg a.s/ha). *On the other hand, the metabolites M6, 2-Carboxybenzaldehyde and 'Unknown 2' failed the risk assessment based on FOCUS Step 2 for all proposed representative uses, which needs to be further addressed.* 

In addition a risk assessment was performed for sediment dwelling organisms exposed to AN (2-amino-1,4naphthoquinone), a degradation product of Quinoclamine which is relevant only in sediment. *Also from this metabolite unacceptable risks were identified for most uses, based on FOCUS Step 2. This needs to be further addressed.* 

#### 2.9.9.3 Summary of product exposure and risk assessment for arthropods

#### Bees

A risk assessment for bees was conducted both according to the EFSA Bee Guidance Document (EFSA Journal 2013;11(7):3295) and the EPPO (2010) scheme (OEPP/EPPO Bulletin 40: 323-331, Chapter 10.

Acceptable acute risks to adult bees could be concluded at the initial screening step, both via contact and oral exposure (EFSA 2013; EPPO 2010). Moreover, a low risk for effects on hypopharyngeal glands of honeybees was demonstrated (EFSA 2013). The risk to honeybees via water consumption was also assessed as acceptable according to EFSA (2013).

Unacceptable chronic risks to adult honeybees and larvae was identified at the initial screening step and these risks were further investigated at Tier 1 according to EFSA (2013). It was concluded that the chronic risk to adult honeybees and larvae exposed to the treated crop was still unacceptable, whereas other routes of exposure (weeds in the treated field, field margin, adjacent crop and following year on a permanent crop or on a succeeding crop for annual crops) did not cause unacceptable risk to honeybees.

It should be noted that both tree nurseries and golf greens are probably less attractive to bees. Golf greens are meticulously cultivated areas (year-round) where presence of flowering weeds at any time is highly unlikely. With regard to outdoor tree nurseries, GAP treatment is restricted to wooden plants, of which very few are likely to be flowering during application. Furthermore, treatment of flowering crop is already excluded in the proposed GAP. Finally, with the exception of tractor-drawn application (1.44 kg ai/ha), contamination of the flower blossom is highly unlikely due to targeted application to the substrate in the planting pot, with weed growth prevented by the soil covering.

Nevertheless, the applicant proposed the following **label restrictions** in order to address the identified risk to foraging honeybees (chronic adult and larvae) within the treated field:

#### Lawns, nursery potted plants:

Dangerous to bees. To protect bees and other pollinating insects do not apply on flowering crops. Do not use where bees are actively foraging.

#### Other arthropods

Tier 1

A risk assessment was performed according to the Guidance document on terrestrial ecotoxicology (SANCO/10329/2002 rev 2 final, 17 October 2002) and the Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods (ESCORT 2, Candolfi et al. 2000).

The available standard laboratory study results as well as the Tier 1 exposure calculations indicated that no unacceptable effects are to be expected from the application of Quinoclamine according to GAP. However, since results from extended laboratory tests were also available, a higher tier risk assessment is presented below.

## Higher tier

Based on the available extended laboratory data for the predatory mite *Typhlodromus pyri* a risk was indicated for non-target arthropods within the treated field, since the calculated in-field exposure exceeded the laboratory ER50 for reproduction. However, in an aged residue study with *Typhlodromus pyri*, an initially reduced reproduction until day 14 was followed by a recovered reproduction within the next 14 days when continuously exposed to the aged residues on the plants. After the 28 days test period no significant effects on reproduction were observed.

Based on the assessment above, it was concluded that acceptable risks to non-target arthropods following the proposed uses of Quinoclamine can be expected.

#### 2.9.9.4 Summary of product exposure and risk assessment for non-target soil meso- and macrofauna

A risk assessment for soil-dwelling organisms was performed according to the Guidance document on terrestrial ecotoxicology (SANCO/10329/2002 rev 2 final, 17 October 2002). Where no toxicity data were available, relevant degradation products were assumed to be 10 times more toxic than the active substance. At a late stage of the evaluation, the applicant proposed that toxicity of the metabolites should be estimated based the approach given in the more recent guidance document for aquatic risk assessment (EFSA 2013). The RMS considers this approach as reasonable, at least as a weight of evidence, but did not revise the risk assessment at this stage. Opinions from other MS would be welcome during the peer review.

#### Tier 1

For the proposed uses of Quinoclamine on golf greens, acceptable risk to earthworms and other macro organisms could be concluded based on Tier 1 laboratory data and also based on additional higher tier field data (grassland).

Based on a Tier 1 risk assessment for nursery stock plants, an unacceptable risk was indicated at the higher application rates for earthworms and springtails (*Folsomia candida*) but not for predatory mites (*Hypoaspis aculeifer*). Acceptable risks to all non-target soil meso- and macrofauna in nursery stock plants could be concluded at Tier 1 following the lowest proposed application rate of 0.81 kg a.s./ha.

#### Higher tier

For a higher tier assessment in nursery stock plants, results from two available field studies with earthworms and other macro organisms were available. The representativeness of these studies for the uses in nursery stock plants has been discussed in Volume 3, Annex B.9 on the representative formulation, section B.9.8.2, but may need to be further discussed considering that both studies were conducted on grassland and that the earthworm field study had a less optimal application timing and that also no analytical verification of the test item concentrations in the soil was performed in this study. If the available higher tier data are considered, though, an acceptable risk to non-target soil meso- and macrofauna following all proposed representative uses of Quinoclamine in nursery stock plants can be concluded.

#### 2.9.9.5 Summary of product exposure and risk assessment for soil nitrogen transformation

The maximum concentrations with no effect (less than 25% on soil nitrogen transformation within maximum 100 days) were compared to the maximum calculated concentration in soil considering the proposed application rates on golf greens and in nursery stock plants respectively. Where no toxicity data were available, relevant degradation products were assumed to be 10 times more toxic than the active substance.

A low risk for effects on soil nitrogen transformation following the proposed uses of Quinoclamine was concluded.

#### 2.9.9.6 Summary of product exposure and risk assessment for terrestrial non-target higher plants

A risk assessment for terrestrial non-target higher plants was performed according to the Guidance document on terrestrial ecotoxicology (SANCO/10329/2002 rev 2 final, 17 October 2002).

The results demonstrated that exposure to non-target higher plants is acceptable without drift reduction technique even at the standard buffer distance of 1 m, when the proposed representative use pattern for Quinoclamine (formulated as Mogeton TOP, i.e. Mogeton 50% WG) is followed.

#### 2.9.9.7 Summary of product exposure and risk assessment for biological methods for sewage treatment

Although effects of 11 - 17% compared to the control were seen at the lowest concentration (10 mg/L) in the available study, it is not considered likely that the recommended use of Quinoclamine will result in contamination of sewage treatment plants at concentration levels that would cause severe effects. Therefore, the risk for harmful effects on biological methods of sewage treatment is considered to be acceptable.

# 2.10 Proposed harmonised classification and labelling according to the CLP criteria

# 2.10.1 Identity of the substance

# 2.10.1.1 Name and other identifiers of the substance

Name(s) in the IUPAC nomenclature or other international	2-amino-3-chloro-1,4-naphthoquinone		
chemical name(s)	2-amino-3-chloro-1,4-naphthalenedione		
Other names (usual name, trade name, abbreviation)	Quinoclamine, ACN, ACNQ, K-1616, Mogeton		
ISO common name (if available and appropriate)	Quinoclamine		
EC number (if available and appropriate)	220-529-2		
EC name (if available and appropriate)	2-amino-3-chloro-1,4-naphthoquinone		
CAS number (if available)	2797-51-5		
Other identity code (if available)	CIPAC no 648		
Molecular formula	C <sub>10</sub> H <sub>6</sub> ClNO <sub>2</sub>		
Structural formula			
SMILES notation (if available)	O=C2c1ccccc1C(=O)C(Cl)=C2N		
Molecular weight or molecular weight range	207.6		
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable		
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable		
Degree of purity (%) (if relevant for the entry in Annex VI)	Minimum purity 96.5 %		

#### 2.10.1.2 Composition of the substance

 Table 2.10.1.2-1. Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi- constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self- classification and labelling (CLP)
Quinoclamine CAS No. 2797-51-5 EC-No. 220-529-2	Min. 96.5%	-	There are five aggregated notifications with a total of 75 notifiers. The main notification comprising 46 notifiers has the following proposal: Acute Tox. 4 Skin Sens. 1 Eye Irrit. 2 Acute Tox. 3 Repr. 2 STOT SE 2 Aquatic Acute 1

RMS: SE	
Co-RMS: DE	

	Aquatic Chronic 1
	The other minor notifications have in most cases less severe classification proposals
	However, STOT RE 2 is
	also added in two instances (a total of 5 notifiers).

#### Table 2.10.1.2-2. Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and	Concentration range (% w/w minimum	Current CLH in Annex VI Table 3.1	Current self- classification and	The impurity contributes to the
numerical identifier)	and maximum)	(CLP)	labelling (CLP)	classification and labelling
Dichlone CAS-No. 117-80-6 EC-No. 204-210-5	Max 1.5 %	Acute Tox. 4 H302 Skin. Irrit. 2 H315 Eye Irrit. 2 H319 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	There are eight aggregated notifications with a total of 191 notifiers. The main notification (66 notifiers) has the same proposal as the harmonised classification except for the addition of Skin Sens. 1 (H317). The other minor notifications has less sever classification proposal except in one instance where Skin Sens. 2 is also added (2 notifers).	No

## Table 2.10.1.2-3. 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
Quinoclamine contains no additives	-	-	-	-	-

# Table 2.10.1.2-4. Test substances (non-confidential information)

Study title	Batch No	Purity
(14C)-Quinoclamine: Absorption, distribution, metabolism and excretion in the rat.	8086	99%
Covance Lab. Ltd., North Yorkshire, England		
Report No. 619/102-D1145		
Report date: 2002-12-23		
GLP, not published		
Quinoclamine: Acute oral toxicity study in the rat	8086	99%
Covance Lab. Ltd., North Yorkshire, England		
Report No. 619/141-D6144		
2002-02-28		
GLP, unpublished		

Study title	Batch No	Purity
Acute oral toxicity of Quinoclamine in rats	3061	98.3%
Public Interest Incorporated Foundation		
Biosafety Research Center (BSRC) 582-2, Shioshinden, Iwata, Shizuoka437-1213, Japan		
Report No. G427 /154-768		
Report date: 2016-01-18		
GLP, unpubulished	0007	0.001
Quinoclamine: Acute dermal toxicity study in the rat	8086	99%
Covance Lab. Ltd., North Yorkshire, England		
Report date: 2002-01-28		
GLP unpublished		
Acute inhalation toxicity in rats $-4$ Hour exposure	5063	98.1%
Huntingdon Research, Cambridgeshire, England	2002	2011/0
Report No. TYC 3786432		
Report date: 1986-08-13		
GLP, unpublished		
Primary skin irritation study	5063	98.1%
Toxicol Laboratories Ltd, Ledbury, Herefordshire, HR8 1LH, England		
Report No. 105/8509		
Report date: 1985-11-22		
GLP, unpublished	5062	00.10/
Primary eye irritation study Taxiaal Laboratoriaa Ltd. Ladhury, Uarafordahira, UDS 1111, England	5063	98.1%
Papert No. 106/8500		
Report date: 1985-11-27		
GIP unpublished		
Ouinoclamine: Skin sensitisation study in the guinea pig	8086	99%
Covance Lab. Ltd., North Yorkshire. England	0000	2270
Report No. 619/119-D6144		
Report date: 2000-12-22		
Non-GLP, unpublished		
Evaluation of in vitro phototoxicity of Quinoclamine technical in 3T3 fibroblasts using	3061	98.3
the Neutral Red uptake assay		
WIL Research Europe, The Netherlands		
Report No. 5087/1		
Report date: 2015-11-1/		
Our of the state o	8086	0.00%
Covance Lab Ltd. North Vorkshire England	8080	<b>99</b> 70
Report No. 619/148		
Report date: 2002-09-06		
GLP, unpublished		
Quinoclamine: 28 day oral (capsule administration) toxicity study in the dog	8086	99%
Covance Lab. Ltd., North Yorkshire, England		
Report No. 619/149		
Report date: 2002-07-04		
GLP, unpublished		
90 Days subacute toxicological test of Mogeton on rat	No data	No data
Tokyo Women's Medical College, Department of Hygiene II		
Report data:		
Non-GLP unpublished		
Outpoclamine: 13 week oral (dietary administration) toxicity study in the rat	8086	99%
Covance Lab. Ltd., North Yorkshire. England	0000	
Report No. 0619/132		
Report date: 2003-03-28		
GLP, unpublished		
Quinoclamine: 13 week oral (capsule administration) toxicity study in the dog	8086	99%
Covance Lab. Ltd., North Yorkshire, England		
Report No. 0619/134		
Report date: 2002-11-12		
GLP, unpublished		

Study title	Batch No	Purity
Ouinoclamine: 28 day (dermal administration) toxicity study in the rat	8086	99%
Covance Lab. Ltd., North Yorkshire, England	0000	2270
Report No. 619/133		
Report date: 2002-09-30		
GLP, unpublished		
Quinoclamine: Reverse mutation in four histidine-requiring strains of Salmonella	8086	99%
typhimurium and one Tryptophan-requiring strain of Escherichia coli.		
Covance Laboratories Ltd., North Yorkshire, UK		
Report No. 619/103-D6171		
Report date: 2002-01-29		
GLP, unpublished		
Metaphase analysis of human lymphocytes treated with ACN technical	5063	98.1%
Toxicol Laboratories Ltd, Ledbury, Herefordshire, HR8 1LH, England		
Report No. 238/8702		
Report date: 1987-09-29		
GLP, unpublished	50.60	00.10/
Tests for gene mutations resistant to Quabain in L5178Y mouse lymphoma cells treated	5063	98.1%
with ACN technical		
I oxicol Laboratories Ltd, Ledbury, Herefordshire, HK8 ILH, England		
Report No. 239/8/02/A		
No CLD uppublished		
No OLF, unpublished	5062	08 10/
Toxical Laboratories Ltd Ledbury Herefordshire HP8 11 H England	5005	90.170
Report No. M/MMN/1582		
Report date: 1987-09-01		
No GLP unpublished		
Ouinoclamine: Measurement of unscheduled DNA Synthesis in rat liver using an in	5081	97.6%
vivo/in vitro procedure	5001	21.070
Corning Hazleton (Europe), North Yorkshire HG3 1PY, England		
Report No. 619/5-1052		
Report date: 1996-11-01		
GLP, unpublished		
ACN-technical 104 week (dietary) combined chronic toxicity and carcinogenicity study	2010	98.3%
in the rat		
Toxicol Laboratories Ltd, Ledbury, Herefordshire, HR8 1LH, England		
Report No. AKJ/7/90		
Report date: 1991-08-30		
No GLP, not published		
ACN Technical, 80-week (dietary) carcinogenicity study in the mouse	8055	98.5%
Toxicol Laboratories Ltd, Ledbury, Herefordshire, HR8 1LH, England		
Report No. AKJ/56/93		
1995-11-17 CID not multiched		
CLP, not published	V 1616	08 50/
Lagleton Laboratorias America Inc. Virginia 22180, USA	K-1010	98.3%
Report No. 854-110		
1976-02-18		
No GLP unpublished		
A two generation reproduction study in rats	K-1616	No data
Hazleton Laboratories America Inc. Virginia 22180. USA	11 1010	110 000
Report No. 854-111		
Report date: 1975-05-30		
No GLP, not published		
Rat Teratology Range Finding Study	5063	98.1%
Toxicol Laboratories Ltd, Ledbury, Herefordshire, HR8 1LH, England		
Report No. AKJ/2/86		
Report date: 1986-06-01		
No GLP, not published		

Study title	Batch No	Purity
ACN (Technical). Rat Teratology Study	5063	98.1%
Toxicol Laboratories Ltd, Ledbury, Herefordshire HR8 1LH, England		
Report No. AKJ/4/86		
Report date: 1986-10-01		
No GLP, not published		
Quinoclamine: Oral (Gavage) Range-finding study of prenatal toxicity in the rat	8086	99%
Covance Laboratories Ltd., North Yorkshire, UK		
Report No. 619/123-D6154		
Report date: 2002-08-19		
GLP, not published	2026	0.00/
Qunoclamine: Oral (Gavage) prenatal developmental toxicity study in the rat	8086	99%
Covarice Laboratories Liu., Harrogate, UK Papart No. 610/04 D6154		
Report date: 2002-08-19		
GLP, not published		
ACN (Technical). Rabbit Teratology range finding study	5063	98.1%
Toxicol Laboratories Ltd, Ledbury, Herefordshire, HR8 1LH, England		2 012 / 0
Report No. AKJ/1/86		
Report date: 1986-06-01		
No GLP, not published		
Addendum to rabbit teratology range finding study	5063	98.1%
Toxicol Laboratories Ltd, Ledbury, Herefordshire, HR8 1LH, England		
Report No. AKJ/1A/89		
Report date: 1989-07-28		
No GLP, not published		
ACN (Technical), Rabbit Teratology Study	5063	98.1%
Toxicol Laboratories Ltd, Ledbury, Herefordshire, HR8 1LH, England		
Report No. AKJ/3/86		
Report date: 1986-10-01		
No GLP, not published	2026	0.00/
Quinoclamine: Oral (Gavage) Range-finding study of prenatal toxicity in the rabbit Coveres Laboratories Ltd. North Verkebirg, UV	8086	99%
Covance Laboratories Ltd., North Forkshile, UK		
Report date: 2002-08-19		
GLP not nublished		
Ouinoclamine: Oral (Gayage) prenatal developmental toxicity study in the rabbit	8086	99%
Covance Laboratories Ltd., North Yorkshire, UK	0000	2270
Report No. 619/155-D6154		
2002-08-19		
GLP, not published		
Quinoclamine: Dermal embryo-foetal development study	4036	97.7%
Corning Hazleton, D-48163 Münster, Germany		
Report No. 1312-1416-001		
Report date: 1996-11-08		
GLP, not published		
Avian single-dose oral LD50 of Mogeton in bobwhite quail	5063	98.1%
Hazleton Laboratories America		
Report No. 6028-602		
CLD uppublished		
5-day diatary toxicity study in bobybite quail with Ouinoclamine technical +	8086	90.0%
Amendments 1+2	0000	JJ.070
Notox Safety & Environmental Research The Netherlands		
Report No. 318869		
Report date: 2001-12-14		
GLP, unpublished		
Avian Dietary Toxicity Test of Quinoclamine Technical on Mallard Duck (Anas	1096	99.8%
platyrhynchos).		
Lab International Research Center Hungary		
Report No. 05/896-113TÖ		
Report date: 2005-08-24		
GLP, unpublished		

Study title	Rotch No	Durity
Reproduction study in boby hits quail with Opinoplaming technical (by distant	8086	
admixtura)	0000	99%
admixture). Notox Safaty & Environmental Decearch. The Natherlands		
Report No. 318015		
Report date: 2002-00-20		
GLP not published		
Acute toxicity fish test (OECD 203) Ouinoclamine Salmo gairdneri	1060	98.5%
+ Lenz (1991) Determination of Ouinoclamine in combination with the acute toxicity fish	1000	20.270
test Salmo gairdneri		
Biochem GmbH.		
Report No. 912043117		
Report date: 1991-10-31		
GLP. unpublished		
Acute toxicity fish test (OECD 203) Ouinoclamine, Brachydanio rerio.	1060	98.5%
+ Lenz (1991) Determination of Ouinoclamine in combination with the acute toxicity fish		
test Brachydanio rerio.		
Biochem GmbH.		
Report No. 912043562		
Report date: 1991-12-17		
GLP, unpublished		
Rainbow trout (Oncorhynchus mykiss), early life stage toxicity test, flow through	3061	98.3%
conditions, test item Quinoclamine		
Fraunhofer Institute IME, Schmallenberg, Germany		
Report No. AGK-001/4-43/E		
Report date: 2015-07-08		
GLP, unpublished		
Document also used as KCA 4.1.2/14		
Prolonged toxicity fish test (OECD Guideline 204) 21-day study Quinoclamine, Salmo	1060	98.5%
gairdneri + Lenz (1991) Determination of Quinoclamine in combination with the		
prolonged toxicity fish test Salmo gairdneri.		
Biochem GmbH.		
Report No. 912043117B		
Report date: 1991-11-19		
GLP, unpublished		
Rainbow Trout (Oncorhynchus mykiss), Early Life Stage Toxicity Test, Flow through	3061	98.3%
conditions		
Acute toxicity in Daphnia magna, test article: Quinoclamin	1060	98.5%
IBR Forschungs GmbH		
Report No. 80-91-1397-10-91		
Report date: 1991-12-10		
GLP, unpublished		
21 d Reproduction test in Daphnia magna	1060	98.5%
IBR Forschungs GmbH, Walsrode, Germany		
Report No. 83-00-0992/00-94		
Report date: 1994-08-25		
GLP, not published		
Effects on larvae of Chironomus riparius in a water-sediment system according to OECD	8033	98.1%
Guideline (Draft 1998) and BBA Guideline (Proposal 1995) Quinoclamin (tech.)		
BioChem agrar, Cunnersdorf, Germany		
Report No. 99 10 48 113		
Report date: 2000-11-14		
GLP, not published	D 10	00.001
Analytical Part: Effects on larvae of Chironomus riparius in a water-sediment system	P-18	99.9%
according to OECD Guideline (Draft 1998) and BBA Guideline (Proposal 1995)		
Quinociamin (tech.)		
Dr. Specht & Partner, Hamburg, Germany		
Report No. 99 10 48 115 – BIO-0005		
Keport date: 2000-06-22		
GLP, not published		

Algae growth inhibition test - test article: Quinoclamin         01/1090         No data           BR, Waltords Germany         01/1090         No data           Report disc: 991-00-28         01/1090         No data           Algae (Navicula pelliculosa) growth inhibition test following OECD 201 (1984) and US (rech.)         8033         98.1%           Machine agar, CumersMarf, Germany         Report disc: 2000-11-15         98.1%         99.9%           Analytical part, Agae (Navicula pelliculosa) growth inhibition test following OECD 201 (1984) and US EPA OPTTS 850.5400 'Algal toxicity. Tiers 1 and IF (Public Draft 1996). Quinoclamin (tech.)         P-18         99.9%           Specht Alg: 2000-11-15         GLP, not published         3061         98.3%           LP, not published         10.43 008         98.1%         99.9%           Specht & Partine, Cannersdorf, Germany         Report Na. B10.0008         98.3%           Report Na. B10.0008         Report Na. B10.0008         98.3%           BioChem agar, Gerichshain, Germany         Report Na. B10.0008         98.1%           Report Na. B10.0008         Report Na. B10.0008         98.10%           BioChem agar, Gerichshain, Germany         Report Na. B10.0008         99.10%           Report Adie: 2015 02.17         GLP, not published         99.10%           Document also used as KCA 4.1.2/16	Study title	Batch No	Purity
ITRE, Walsrode, Germany       International Control (1984)       International Control (1984)         Report Na. 80031-0045(05:53)       Report date: 1994-02-28       S033       98.1%         CILP, not published       S033       98.1%       S033       98.1%         EPA OPPTS 850.5400 'Algal toxicity, Tires I and II' (Public Draft 1996). Quinoclamin (tech.)       BioChem agar. Characterologic, Germany       S033       98.1%         Report No. 99 10 48 121       Report date: 2000-11-15       GILP, and published       P-18       99.9%         Quinoclamin (tech.)       Specht & Partner, Chancesdoff, Germany       Report date: 2000-10-31       P-18       99.9%         Quinoclamin (tech.)       Specht & Partner, Chancesdoff, Germany       Specht & Partner, Chancesdoff, Germany       Specht & Partner, Chancesdoff, Germany         Report date: 2000-10-31       GLP, not published       3061       98.3%         Document also conditions       Germany       Specht & Partner, Chancesdoff, Germany         Report date: 2001-10-31       GLP, not published       3061       98.3%         Document also conditions       Germany       Specht & Partner, Chancesdoff, Germany         Report date: 2001-01-31       GLP, not published       3061       98.10%         Lemna minor growth inhibition test following OECD ringtest guideline (version 1997)       8033	Algae growth inhibition test – test article: Ouinoclamin	01/1090	No data
Report No. 80-91-0045365-93         Report date: 1994-02-28         8033         98.1%           GLP, not published         8033         98.1%         8033         98.1%           EPA OPTIS 850-5400 'Algal toxicity, Tiers I and II' (Public Draft 1996). Quinoclamin (tech.)         8033         98.1%           BioChem agrar, Cumersdorf, Germany         Report No. 90 104 8121         99.9%         99.9%           CH2P, not published         99.9%         99.9%         99.9%           Ottomolamin (tech.)         Spech & Portzen, Cumersdorf, Germany         89.16%         99.9%           Report No. BLO-0008         80040 'Algal toxicity, Tiers I and II' (Public Draft 1996).         91.8         99.9%           Option Vo. BLO-0008         80040 'Algal toxicity, Tiers I and II' (Public Draft 1996).         91.8         99.9%           Cl2P, not published         3061         98.3%         98.10%         8833         98.10%           Effects of Quinoclamin (tech.)         Report No. 110.4104 5008         8033         98.10%         98.10%           Report Mate: 2015-02-17         GL2P, not published         3061         98.3%         98.10%           IP OPHIC Draft 1996). Quinoclamin (tech.).         Report Mate: 2001-11-14         80.400 'Aquatic plant toxicity test using Lemma spp. Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).         99.90%	IBR, Walsrode, Germany	01,10,0	110 4444
Report date: 1994-02-28         8033           GLP. not published         8033           Algae (Navicula peliculosa) growth inhibition test following OECD 201 (1984) and US         8033           BiChem agart, Cumersdorf, Germany         8037           Report nate: 2000-11-15         99.9%           CIPA OPERS 850.5400 'Algal toxicity, Tiers I and IF' (Public Draft 1996). Quinoclamin (tech.)         99.9%           Spech: & Partner, Cumersdorf, Germany         99.9%           Report nate: 2000-10-13         99.9%           Quinoclamin (tech.)         3061         98.3%           BiChem agart, Gernkshain, Germany         8033         98.1%           Report date: 2001-0-31         99.9%         99.9%           GLP, not published         3061         98.3%           BiChem agart, Gernkshain, Germany         8033         98.10%           Report date: 2001-0-31         8033         98.10%           GLP, not published         2001-0-31         98.3%           Document also used as KCA 4.1.216         8033         98.10%           Leman atminor growth inhibition test following OECD ringtest guideline (version 1997) and US EPA OPTYS 850.4400 'Aquatic platt toxicity test using Lemna spp. Tiers I and IF (Public Draft 1996). Quinoclamin (tech.).         8033         98.10%           BiOchem agar, Germany         Per18	Report No. 80-91-0045/05-93		
GLP, not published       98.1%         Algae (Navicula pelliculosa) growth inhibition test following OECD 201 (1984) and US EPA OPPTS 850.5400 'Algal toxicity, Tiers I and II' (Public Draft 1996). Quinoclamin (tech.)       8033       98.1%         BioChem agrar, Cumersdorf, Germany Report No. 99 10 48 121       99.9%       99.9%         Analytical part: Algae (Navicula pelliculosa) growth inhibition test following OECD 201 (1984) and US EPA OPPTS 850.5400 'Algal toxicity, Tiers I and II' (Public Draft 1996). Quinoclamin (tech.)       P-18       99.9%         Specht & Partner, Cumersdorf, Germany Report No. B10-0008       8031       98.3%         Report date: 2000-10-31       3061       98.3%         BioChem agrar, Gerichshain, Germany Report No. B10-0408       8033       98.10%         Report date: 2015-02-17       GLP, not published       3061       98.3%         Document also used as KCA 4.1.2/16       8033       98.10%         Document also used as KCA 4.1.2/16       8033       98.10%         I' Orbbic Draft 1996). Quinoclamin (tech.).       8033       98.10%         BioChem agrar, Germahy Report No. 91 04 81 122       89.90%       99.90%         Report date: 2000-01-13       121       8033       98.10%         GLP, not published       99.90%       99.90%       99.90%         Outnoclamine technical: Sublehal toxicity or Quinoclamin (tech.).	Report date: 1994-02-28		
Algae (Navicula peliculosa) growth inhibition test following OECD 201 (1984) and US       8033       98.1%.         IPA OPPTS 850.5400 'Algal toxicity, Tiers I and II' (Public Draft 1996). Quinoclamin (tech.)       8033       98.1%.         BioChem agrar, Cunnersdorf, Germany       99.9%       99.9%       99.9%         Report Ont: 2000-11-15       99.9%       99.9%       99.9%         Quinoclamin (tech.)       Stocker (Ange (Navicula peliculosa) growth inhibition test following OECD 201       P-18       99.9%         Quinoclamin (tech.)       Specht & Partner, Cunnersdorf, Germany       8033       98.3%         Report No. BIO-0008       Report date: 2000-10-31       98.3%       98.3%         BioChem agrar, Cerichshain, Germany       8001-00-031       98.3%         Report No. 14 10 48 008 W       8033       98.10%         Report date: 2001-10-31       99.90%       98.10%         Document also used as KCA 4.12/16       8033       98.10%         Lemna minor growth inhibition test following OECD ringtest guideline (version 1997) and US EPA OPPTS 850.4400 'Aquatic plant toxicity test using Lemna spp. Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).       8033       98.10%         Report No. 19 10 48 122       Report date: 2000-91-31       99.90%       99.90%       99.90%         ClP, not published       00.4122       Not Hobik Draft 199	GLP, not published		
EPA OPPTS 850.5400 'Algal toxicity, Tiers I and II' (Public Draft 1996). Quinoclamin (tech.)       Particle Part Part Part Part Part Part Part Part	Algae (Navicula pelliculosa) growth inhibition test following OECD 201 (1984) and US	8033	98.1%
(tech.)       BioChem agar. Cunnersdorf, Germany         Report No. 99 10 48 121       Peport date: 2000-11-15         GLP, not published       P-18         Analytical part: Algae (Nevicula pelliculosa) growth inhibition test following OECD 201       P-18         Quinoclamin (tech.)       Specht & Partner, Cunnersdorf, Germany         Report full: 2000-10-31       GEP, not published         Fffects of Quinoclamin technical on Myriophyllum spicatum in a growth inhibition test       3061         Inffects of Quinoclamin technical on Myriophyllum spicatum in a growth inhibition test       3061         BioChem agar, Gerichabian, Germany       Report date: 2015-02-17         GLP, not published       Document also used as KCA 4.1.2/16         Document also used as KCA 4.1.2/16       Document also used as KCA 4.1.2/16         Lemma minor growth inhibition test following OECD ringtest guideline (version 1997)       8033         and UF Quinoclamin (tech.).       Specified and the process of the p	EPA OPPTS 850.5400 'Algal toxicity, Tiers I and II' (Public Draft 1996). Quinoclamin		
BioChem agrar, Cunnersdorf, Germany         Report No. 99 1048 121         Report Atac: 2000-11-15         CUP, not published         Analytical part: Algae (Navicula pelliculosa) growth inhibition test following OECD 201         (1984) and US EPA OPPTS 850.5400 'Algal toxicity, Tiers I and II' (Public Draft 1996).         Quinoclamin (tech.)         Specht & Partner, Cunnersdorf, Germany         Report No. B10-0008         Report No. B10-0008         Report No. 101-031         Elfects of Quinoclamine technical on Myriophyllum spicatum in a growth inhibition test         BioChem agrar, Gerichshain, Germany         Report No. 11 04 8008         Report No. 11 04 4008         Report No. 14 10 48008         Report Als: 2015-02-17         GLP, not published         Document also used as KCA 4,1,2/16         Lemma minor growth inhibition test following OECD ringtest guideline (version 1997)         and US EPA OPPTS S50.4400 'Aquatic plant toxicity test using Lemma spp. Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).         Specht & Partper, Hamburg, Germany         Report No. 10408 6075         Report No. 1040	(tech.)		
Report No. 99 10 48 121         P-18         99.9%           GLP, not published         P-18         99.9%           Analytical part: Algae (Navicula pelliculosa) growth inhibition test following OECD 201 (1984) and US FPA OPPTS 850.5400 'Algal toxicity, Tiers I and II' (Public Draft 1996). Quinoclamin (ech.)         P-18         99.9%           Specht & Parmer, Cunnersdorf, Germany Report No. B10-0008         Specht & Parmer, Cunnersdorf, Germany         Specht Specht & Parmer, Cunnersdorf, Germany         Specht Specht & Parmer, Cunnersdorf, Germany           Report No. 14 10 48 008 W         Report Ale: 2015-02-17         Specht Specht & Parmer, Gerichshain, Germany         Specht Specht & Sp	BioChem agrar, Cunnersdorf, Germany		
Report date: 2000-11-15         ClP, not published         99.9%           Analytical par: Algae (Navicula pelliculosa) growth inhibition test following OECD 201         P-18         99.9%           (1984) and US EPA OPPTS 850.5400 'Algal toxicity, Tiers I and II' (Public Draft 1996).         98.3%         98.3%           Specht & Partner, Cunnersdorf, Germany         8061         98.3%         98.3%           Report No. BIO-0008         Report No. BIO-0008         8061         98.3%           Report No. II 0.43 00 SW         8063         98.3%         98.10%           BioChem agrar, Gerichshain, Germany         8033         98.10%         98.10%           Document also used as KCA 4.12.16         8033         98.10%           Lemna minor growth inhibition test following OECD ringtest guideline (version 1997)         8033         98.10%           II' (Public Draft 1996). Quinoclamin (tech.).         BioChem agrar, Gerichshain, Germany         8033         98.10%           Report No. 99 10 48 122         Report date: 2000-11-14         99.90%         99.90%         99.90%           Verbitio Darit 1996). Quinoclamin (tech.).         Sinchemagra, Gerichshain, Germany         8033         98.10%           Specht & Partpner, Hamburg, Germany         Report date: 2000-11-14         99.90%         99.90%           GLP, not published         Notio	Report No. 99 10 48 121		
LLP, not published         99.9%           Analytical part: Algae (Navicula pelliculosa) growth inhibition test following OECD 201 (1984) and US EPA OPPTS 850.5400 'Algal toxicity, Tiers I and II' (Public Draft 1996). Quinoclamin (ech.)         99.9%           Specht & Partner, Cunnersdorf, Germany Report No. BIO-0008         8         98.3%           Effects of Quinoclamin technical on Myriophyllum spicatum in a growth inhibition test under semi-static test conditions         3061         98.3%           BioChem agrar, Gerichshain, Germany Report No. 14 10 48 008 W         8033         98.10%           UP (Published Document also used as KCA 4.1.2/16         8033         98.10%           Lemma minor growth inhibition test following OECD ringtest guideline (version 1997) and US EPA OPPTS 880.4400 'Aquatic plant toxicity test using Lemma spp., Tiers I and II' (Public Draft 1996), Quinoclamin (tech.).         8033         98.10%           GLP, not published         99.90%         99.90%         99.90%           Analytical part: Lemma minor growth inhibition test following OECD ringtest guideline (version 1997) and US EPA OPPTS 880.4400 'Aquatic plant toxicity test using Lemma spp., Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).         99.90%           Spect No. 80 10-005         Report No. 810-005         80040 'Aguatic plant toxicity test using Lemma sp., Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).         99.90%           GLP, not published         99.90%         99.90%         99.28%         99.90%	Report date: 2000-11-15		
Analytical part: Argae (Navicula peliculosa) growth inhibition test following OELD 201       P-18       99,9%         (1984) and US EPA OPPTS 850.5400 'Algat toxicity, Tiers I and II' (Public Draft 1996).       Specht & Partner, Cunnersdorf, Germany       Specht & Partner, Cunnersdorf, Germany         Report No. BIO-0008       Report date: 2000-10-31       3061       98.3%         CiLP, not published       3061       98.3%         BioChem agrar, Gerichshain, Germany       Report No. 11 0 48 008 W       8033       98.10%         Report No. 14 10 48 008 W       Report Ada:: 2015-02-17       8033       98.10%         CLP, not published       Document also used as KCA 4.1.2/16       8033       98.10%         Lemma minor growth inhibition test following OECD ringtest guideline (version 1997) and US EPA OPPTS 830.4400 'Aquatic plant toxicity test using Lemma spp., Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).       8033       98.10%         Specht & Partpner, Hamburg, Germany       Report No. BIO-005       PortTS 830.4400 'Aquatic plant toxicity test using Lemma spp., Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).       Specht & Partpner, Hamburg, Germany         Report No. BIO-005       Report No. BIO-005       PortTS 83.0400 'Aquatic plant toxicity test using Lemma spp., Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).       Specht & Partpner, Hamburg, Germany         Report No. BIO-005       Report No. BIO-005       Port No. BIO-005       Po	GLP, not published	D 10	00.00/
(1)999) and US EPA OPT IS 50.3-04 (Vagat toXeny, Tiers I and II (Public Dialt 1990).	Analytical part: Algae (Navicula pelliculosa) growth inhibition test following OECD 201 (1084) and US EDA ODDTS 850 5400 (Algal toxicity, Tiore Land II' (Dublic Droft 1006)	P-18	99.9%
Quinclamin (etc.)       Specht & Partner, Cunnersdorf, Germany         Report No. BIO-0008       Report Ada: 2000-10-31         GLP, not published       3061         Effects of Quinoclamine technical on Myriophyllum spicatum in a growth inhibition test under semi-static test conditions       3061         BioChem agrar, Gerichshain, Germany       8033         Report No. 14 10 48 008 W       8033         Report No. 14 10 48 008 W       8033         Report Ada: 2015-02-17       8033         ClP, not published       8033         Document also used as KCA 4.1.2/16       8033         Lemma minor growth inhibition test following OECD ringtest guideline (version 1997) and US EPA OPPTS 850.4400 'Aquatic plant toxicity test using Lemna spp. Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).         Specht & Partner, Hamburg, Germany       8033         Report No. 99 10 48 122       8004 dat: 2000-91-14         GLP, not published       P-18         Analytical part: Lemna minor growth inhibition test following OECD ringtest guideline (version 197) and US EPA OPPTS 850.4400 'Aquatic plant toxicity test using Lemna spp. Tiers I and II' (Public Draft 1996). Quinoclamin (tech.).         Specht & Partner, Hamburg, Germany       8004         Report No. BIO-005       8004         Report No. BIO-005       8004         Report Ata: 2000-10-13       GLP, not published	(1984) and US EFA OFF IS 850.5400 Algal toxicity, Tiels I and II (Fublic Dialt 1990).		
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# 2.10.2 Proposed harmonized classification and labelling

## 2.10.2.1 Proposed harmonised classification and labelling according to the CLP criteria

Proposed harmonised classification and labelling according to the CLP criteria

					Classification		Labelling			George Contraction of the second seco	T
	Index No	International Chemical Identification	EC No	CAS No	Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)	Conc. Limits, M-factors	Notes
Current Annex VI entry					No cu	ırrent Annex VI	entry				
Dossier submitters proposal	TBD	quinoclamine (ISO); 2- amino-3-chloro-1,4- naphthoquinone	220- 529-2	2797- 51-5	Carc. 2 Repr. 2 Acute Tox. 4 Eye Irrit. 2 Skin Sens. 1A STOT RE 2 Aquatic Acute 1 Aquatic Chronic 1	H351 H361d H302 H319 H317 H373 (blood system, kidneys) H400 H410	GHS07 GHS08 GHS09 Wng	H351 H361d H302 H319 H317 H373 (blood system, kidneys) H410		oral: ATE = 500 mg/kg bw M=10 M=10	

# 2.10.2.2 Additional hazard statements / labelling

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

# 2.10.3 History of the previous classification and labelling

Quinoclamine is not yet subject to harmonised classification.

# 2.10.4 Identified uses

Quinoclamine is an active substance used in plant protection products which is currently re-evaluated under Regulation 1107/2009. It is used as an herbicide/algaecide for post-emergence control of common mosses and algae occurring on golf greens and of liverwort occurring on the substrate of nursery stock plants.

# 2.10.5 Data sources

Quinoclamine was included in Annex I of EU Council Directive 91/414/EEC on 1<sup>st</sup> January 2009 (Commission Directive 2008/66/EC of 30 June 2008), and was subsequently approved under Regulation (EC) No. 1107/2009 (repealing Council Directive 91/414/EEC) via Commission Implementing Regulation (EU) No. 540/2011 of 25<sup>th</sup> May 2011.

Quinoclamine is currently being re-evaluated under the following regulations for renewal of approval as an active substance in plant protection products:

- REGULATION (EC) No 1107/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.
- COMMISSION IMPLEMENTING REGULATION (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market.

The data presented in this dossier have been submitted by one applicant (Agro-Kanesho Co. Ltd.) as part of the renewal process. Some of the data were submitted and evaluated during the first approval while other data was submitted for the first time for the purpose of renewal of approval.

# 2.11 Relevance of metabolites in groundwater

# 2.11.1 STEP 1: Exclusion of degradation products of no concern

No metabolites were excluded for this reason.

# 2.11.2 STEP 2: Quantification of potential groundwater contamination

PECgw for the representative uses on golf greens and nurseries were available for quinoclamine and products observed in study on photochemical transformation in soil (Adam, 2016a): M6, M9, M10 and M11.

PECgw for the parent compound and the transformation products were  $\leq 0.000$  for all scenarios.

## 2.11.3 STEP 3: Hazard assessment – identification of relevant metabolites

## 2.11.3.1 STEP 3, Stage 1: screening for biological activity

Not required.

## 2.11.3.2 STEP 3, Stage 2: screening for genotoxicity

Not required.

# 2.11.3.3 STEP 3, Stage 3: screening for toxicity

Not required.

# 2.11.4 STEP 4: Exposure assessment – threshold of concern approach

Not required.

# 2.11.5 STEP 5: Refined risk assessment

Not required.

#### 2.11.6 Overall conclusion

Due to the very low PECgw an assessment of the relevance of the transformation products M6, M9, M10 and M11 was not necessary.

## 2.12 Consideration of isomeric composition in the risk assessment

Not relevant as Quinoclamine does not consist of any stereoisomers.

## 2.12.1 Identity and physical chemical properties

Not relevant, see 2.12.

#### 2.12.2 Methods of analysis

Not relevant, see 2.12.

## 2.12.3 Mammalian toxicity

Not relevant, see 2.12.

# 2.12.4 Operator, Worker, Bystander and Resident exposure

Not relevant, see 2.12.

## 2.12.5 Residues and Consumer risk assessment

Not relevant, see 2.12.

# 2.12.6 Environmental fate

Not relevant, see 2.12.

## 2.12.7 Ecotoxicology

Not relevant, see 2.12.

# 2.13 Residue definition

## 2.13.1 Definition of residues for exposure/risk assessment

Food of plant origin: Not relevant for the representative use.

Food of animal origin: Not relevant for the representative use.

Soil: Quinoclamine, M6, M9, M10 and M11.

Groundwater: Quinoclamine, M6, M9, M10 and M11.

Surface water: Quinoclamine, M6, M9, M10, M11, 2-carboxybenzaldehyde and Unknown 2.

Sediment: Quinoclamine, M6, M9, M10, M11 and metabolite AN.

Air: Quinoclamine

## 2.13.2 Definition of residues for monitoring

Food of plant origin: Not relevant for the representative use.

Food of animal origin: Not relevant for the representative use.

Soil: Quinoclamine

Groundwater: Quinoclamine

Surface water: Quinoclamine

Sediment: Quinoclamine

Air: Quinoclamine

#### 2.14 Effect of water treatment processes on the nature of residues present in surface water

During check of completeness of the dossier the RMS asked the applicant to "address the effect of water treatment processes on the nature of residues present in surface water when surface water is abstracted for drinking water. Probably in the first instance, a consideration of the processes of ozonation and chlorination would appear appropriate. If an argumentation is made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be in surface water, as well as the active substance. Should this consideration indicate that novel compounds might be expected to be formed from water treatment, then the risk to human or animal health through the consumption of drinking water containing them should be addressed."

In response, the applicant provided data to show that concentrations of quinoclamine and its metabolites and transformation products will be low at the point of abstraction for drinking water. Available PECsw at which no risk to aquatic organisms was identified were used as a starting point. Corresponding PECgw were calculated using the software Exposit from the German UBA. The model assumes dilution of PECsw in running water and then calculation of PECgw in a bank infiltration step. Maximum PECgw at the drinking water abstraction sites were calculated to  $\leq 0.0028 \ \mu g/L$ . The RMS is unfamiliar with the model EXPOSIT ver 3.01 but according to information at the BVL web-site the model is used for national authorisation in Germany to estimate exposure in groundwater and surface water. It is not an agreed model at the EU level.

The applicant apparently misunderstood the request. There was no attempt to consider the potential effect of water treatment on the nature of possible residues in water, such as the potential for formation of genotoxic compounds. Hence, the submitted study does not address the concern mentioned in Regulation (EC) 1107/2009 art. 4.3 b. A data gap is therefore identified, but in the absence of guidance at the EU level it may be less useful to request further data.

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# Level 3

- **3 Proposed decision with respect to the application**
- 3.1 Background to the proposed decision
- 3.1.1 Proposal on acceptability against the approval criteria Article 4 and Annex II of Regulation (EC) No 1107/2009


## APPENDICES

## Appendix 1 Guidance documents used in this assessment

Candolfi M.P., Barrett K.L., Campbell P.J., Forster R., Grandy N., Huet M-C., Lewis G., Oomen P. A., Schmuck R. and Vogt H., 2000. Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. From the ESCORT 2 workshop, Wageningen, 21-23 March 2000.

ECHA (European Chemicals Agency), 2017. Guidance on the Application of the CLP Criteria; Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Version 5.0, July 2017.

EFSA (European Food Safety Authority), 2009. Guidance Document on Risk Assessment for Birds and Mammals. EFSA Journal 2009; 7(12):1438.

EFSA (European Food Safety Authority), 2012. Guidance Document on Dermal Absorption. EFSA Journal 2012; 10(4):2665.

EFSA (European Food Safety Authority), 2013. EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera, Bombus spp.* and solitary bees). EFSA Journal 2013;11(7):3295.

EFSA (European Food Safety Authority), 2013. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290.

EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014, 12(10):3874.

EPPO/OEPP, 2010. Environmental risk assessment scheme for plant protection products; Chapter 10: Honeybees (PP 3/10(3)). Bulletin OEPP/EPPO Bulletin 40: 323-331.

European Commission, 2000. Residues: Guidance Document for Generating and Reporting Methods of Analysis in Support of Pre-Registration data Requirements for Annex II (part A, Section 4) and Annex III (part A, section 5) of Directive 91/414. SANCO/3029/99 - rev. 4, 11 July 2000.

European Commission, 2001. Guidance for the setting of an acute reference dose (ARfD). 7199/VI/99 - rev 5, 5 July 2001.

European Commission, 2002. Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC. SANCO/10329/2002 - rev.2 final, 17 October 2002.

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European Commission, 2006. Draft Guidance for the setting and application of acceptable operator exposure levels (AOELs) SANCO/7531 - rev.10, 7 July 2006.

European Commission, 2009. Guidance Document on the Assessment of the Equivalence of Technical Materials of Substances Regulated under Regulation (EC) No 1107/2009. SANCO/10597/2003 - rev. 10.1, 13 July 2012.

European Commission, 2010. Guidance document on residue analytical methods. SANCO/825/00 - rev. 8.1, 16 November 2010.

FOCUS, 1997. Soil persistence models and EU registration. SANCO/7617/VI/96.

FOCUS, 2000. FOCUS Groundwater Scenarios in the EU review of active substances. Report of the FOCUS Groundwater Scenarios Workgroup, EC Document Reference SANCO/321/2000-rev.2. 202 pp, as updated by the Generic Guidance for FOCUS groundwater scenarios, version 1.1 dated April 2002.

FOCUS, 2001. FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC. Report of the FOCUS Working Group on Surface Water Scenarios, EC Document Reference SANCO/4802/2001-rev.2. 245 pp., as updated by the Generic Guidance for FOCUS surface water scenarios, version 1.1 dated March 2012.

FOCUS, 2006. Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 2.0, 434 pp, as updated by the Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration, version 1.1, 2014.

FOCUS, 2007. Landscape and Mitigation Factors In Aquatic Risk Assessment. Volume 1. Extended Summary and Recommendations. Report of the FOCUS Working Group on Landscape and Mitigation Factors in Ecological Risk Assessment, EC Document Reference SANCO/10422/2005 v2.0. 169 pp.

FOCUS, 2014. Generic guidance for Tier 1 FOCUS ground water assessments, version 2.2. FOCUS groundwater scenarios working group

FOCUS, 2014. Generic guidance for FOCUS Surface water scenarios. Version 1.3.

Appendix 2 Reference list