REGULATION (EC) NO 1272/2008 (CLP REGULATION),

ANNEX VI, PART 2

Proposal for Harmonised Classification and Labelling for a biocidal active substance

CLH REPORT

Sodium pyrithione;
Pyridine-2-thiol 1-oxide, sodium salt;
pyrithione sodium

EC Number: 223-296-5; 240-062-8

CAS Number: 3811-73-2; 15922-78-8

Index Number: -

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Version number: 2 Date: March 2019

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STATEMENT OF SUBJECT MATTER AND PURPOSE OF THE CAR

Not applicable for the CLH report.

BPC OPINION

Not applicable for the CLH report.

ASSESSMENT REPORT

SUMMARY

1. PRESENTATION OF THE ACTIVE SUBSTANCE

1.1 IDENTITY OF THE ACTIVE SUBSTANCE

Table 1.1 Main constituents

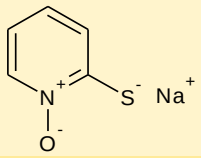
Main constituent(s)	
ISO name	Non assigned
IUPAC or EC name	Sodium pyrithione; Pyridine-2-thiol 1-oxide, sodium salt; sodium 2-sulfanylidene-1,2-dihydropyridin-1-olate
EC number	223-296-5[1]; 240-062-8[2]
CAS number	3811-73-2[1]; 15933-78-8[2]
Index number in Annex VI of CLP	-
Minimum purity / content	>39% (the substance is placed on the market as a 40% aqueous solution; defined as a technical concentrate in accordance with BPR Guidance) >96.5% (calculated dry weight purity)
Structural formula	

Table 1.2 Relevant impurities and additives

Relevant impurities and additives		
IUPAC name or chemical name or EC name	Maximum concentration in % (w/w)	Index number in Annex VI of CLP
None of the impurities are considered relevant for classification.		

1.2 INTENDED USES AND EFFECTIVENESS

Table 1.3 Use of the active substance

Product type	
Intended use pattern(s)	PTs 2, 6, 7, 9, 10, and 13
Users	Professionals and non-professionals

Table 1.4 Effectiveness of the active substance

Function	
Organisms to be controlled	Bacteria, moulds, yeast, actinomycetes
Limitation of efficacy including resistance	*<assessment pending>*
Mode of action	Pyrithione acts on microbial membranes to eliminate certain ion gradients that are used by bacteria to store energy and by fungi as the source of energy for nutrient transport.

[1] The EC/CAS-No. used for the active substance under BPR.
[2] EC/CAS-No. found in CLP-inventory, EC-inventory and in REACH Annex III inventory and pre-registration process. Appears to relate to the same substance.

2. PROPOSED HARMONISED CLASSIFICATION AND LABELLING OF THE ACTIVE SUBSTANCE ACCORDING TO THE CLP CRITERIA

2.1 PROPOSED HARMONISED CLASSIFICATION AND LABELLING FOR THE ACTIVE SUBSTANCE

Table 2.1 Proposed harmonised classification and labelling of the substance

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors, ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal		Sodium pyrithione; Pyridine-2-thiol 1-oxide, sodium salt; pyrithione sodium	223-296-5; 240-062-8	3811-73-2; 15933-78-8	Acute Tox. 4 Acute Tox. 4 Acute Tox. 3 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1 STOT RE 1 Aquatic Acute 1 Aquatic Chronic 2	H302 H312 H331 H315 H319 H317 H372 (mortality, neuromuscular system) H400 H411	GHS06 GHS08 GHS09 Dgr	H302 H312 H331 H315 H319 H317 H372 H410	EUH070	Oral: ATE = 500 mg/kg bw Dermal: ATE = 1800 mg/kg bw Inhalation: ATE = 0.5 mg/L (dusts and mists) M=100	
Resulting Annex VI entry if agreed by RAC and COM		Sodium pyrithione; Pyridine-2-thiol 1-oxide, sodium salt; pyrithione sodium	223-296-5; 240-062-8	3811-73-2[1]; 15933-78-8[2]	Acute Tox. 4 Acute Tox. 4 Acute Tox. 3 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1 STOT RE 1 Aquatic Acute 1 Aquatic Chronic 2	H302 H312 H331 H315 H319 H317 H372 (mortality, neuromuscular system) H400 H411	GHS06 GHS08 GHS09 Dgr	H302 H312 H331 H315 H319 H317 H372 H410	EUH070	Oral: ATE = 500 mg/kg bw Dermal: ATE = 1800 mg/kg bw Inhalation: ATE = 0.5 mg/L (dusts and mists) M=100	

Table 2.2 Reason for not proposing harmonised classification and labelling and the status under CLH public consultation

Hazard class	Reason for not proposing classification and labelling	Within the scope of public consultation
Explosives	Data 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	Data conclusive but not sufficient for classification	Yes
Self-reactive substances and mixtures	Data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Data conclusive but not sufficient for classification	Yes
Self-heating substances and mixtures	Data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	Yes
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Data conclusive but not sufficient for classification	Yes
Organic peroxides	Hazard class not applicable	No
Corrosive to metals	Data conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	Harmonised classification is proposed	Yes
Acute toxicity via dermal route	Harmonised classification is proposed	Yes
Acute toxicity via inhalation route	Harmonised classification is proposed	Yes
Skin corrosion/irritation	Harmonised classification is proposed	Yes
Serious eye damage/eye irritation	Harmonised classification is proposed	Yes
Respiratory sensitisation	Hazard class not assessed	No
Skin sensitisation	Harmonised classification is proposed	Yes
Germ cell mutagenicity	Data conclusive but not sufficient for classification	Yes
Carcinogenicity	Data conclusive but not sufficient for	Yes

	classification	
Reproductive toxicity	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-single exposure	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-repeated exposure	Harmonised classification is proposed	Yes
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Harmonised classification is proposed	Yes
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

2.2.1 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Currently sodium pyrithione does not have a harmonised classification and labelling. It was neither proposed for classification earlier nor discussed by the TC C&L (Dir. 67/548/EE C).

2.2 PROPOSED CLASSIFICATION AND LABELLING AND PACKAGING FOR THE REPRESENTATIVE PRODUCT(S)

Not applicable for the CLH report.

2.3 DATA SOURCES

A dossier was submitted to Sweden as the Rapporteur Member State (now referred to as the evaluating Member State) by the European Sodium Pyrithione Task Force for review of sodium pyrithione as an active substance under the Biocidal Products Directive (Directive 98/8/EC) (now replaced by the Biocidal Products Regulation (Regulation (EU) 528/2012)). This CLH report has been prepared based on the data on sodium pyrithione that was submitted in that dossier and evaluated by Sweden in the draft biocides Competent Authority Report (CAR) that had the following structure

- **Assessment Report**
- **Doc II Risk Assessment**
  Doc IIA: Effects assessment of active substance
  Doc IIB: Effects and exposure assessment of biocidal product(s)
  Doc IIC: Risk Characterisation for use of active substance in biocidal product(s)
- **Doc III: Study Summaries**
  Doc IIIA: Active substance
  Doc IIIB: Biocidal product(s)

Furthermore, information from a dossier dated 27 July 2017 on sodium pyrithione submitted by an applicant as part of their BPR (Regulation (EU) 528/2012) Article 95 notification of the substance, and relevant information from REACH registration dossier(s) for sodium pyrithione is also considered in this CLH report.

The Dossier Submitter (DS) acknowledges that sodium pyrithione shows some structural similarity to zinc pyrithione (EC 236-671-3) and copper pyrithione (238-984-0), in that they share the common organic moiety i.e. pyrithione. However, each of these pyrithione species has distinct physicochemical and toxicological properties. Therefore, the DS does not use grouping and/or read-across in the CLH proposal for sodium pyrithione.

3. SUMMARY OF THE HUMAN HEALTH RISK ASSESSMENT

Not applicable for the CLH report.

4. SUMMARY OF THE ENVIRONMENTAL RISK ASSESSMENT

Not applicable for the CLH report.

5. ASSESSMENT OF EXCLUSION CRITERIA, SUBSTITUTION CRITERIA AND POP

Not applicable for the CLH report.

A. Assessment of intrinsic properties and effects of the active substance

A.1. General substance information

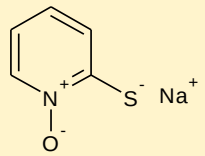
A.1.1. Identity of the substance

Table A.1 Summary table on substance identity

Summary table on substance identity	
Common name (ISO name, synonyms)	Non assigned
Chemical name (EC name, CA name, IUPAC name)	Pyridine-2-thiol 1-oxide, sodium salt; Sodium pyrithione; sodium 2-sulfanylidene-1,2-dihydropyridin-1-olate
EC number	223-296-5[3]; 240-062-8[4]
CAS number	3811-73-2[1]; 15933-78-8[2]
other CAS numbers (e.g. deleted, related, preferred, alternate)	-
Molecular formula	$C_5H_5NOS.Na$
Molecular weight or molecular weight range	149.16 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable, the substance does not contain any stereoisomers.
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable; it is not an UVBC-substance

Table A.2 Structural formula

[3] The EC/CAS-No. used for the active substance under BPR
[4] EC/CAS-No. found in CLP-inventory, EC-inventory and in REACH Annex III inventory and pre-registration process. Appears to relate to the same substance

Structural formula


A.1.2. Composition of the substance (reference specifications)

Table A.3 Main constituents

Main constituent(s)					
Constituent (chemical name)	Typical concentration (%(w/w))	Concentration range (%(w/w))	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	Remarks / Discussion
Sodium pyrithione	>39%* >96.5%**	-	-	See ECHA C&L Inventory[5]	-

* Relates to the substance as produced and placed on the market (aqueous solution)
** Theoretical dry weight purity (calculated)

Table A.4 Impurities
The substance does not contain any impurities that are considered relevant for the classification.

Table A.5 Additives
The substance does not contain any additives.

Table A.6 Concentration of constituents (main constituents, impurities, additives) in batches used for (eco)toxicity studies and proposed specification
The DS considers that the test substance in all the (eco)toxicity studies presented in this report as relevant to the CLH proposal.

[5] https://echa.europa.eu/regulations/clp/cl-inventory

A.1.3. Physical and chemical properties of the active substance

Table A.7 Physical and chemical properties of the active substance

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Aggregate state at 20°C and 101.3 kPA	Solid; lumps; clods (92.5% purity, 7.5% water) Powder (40% aqueous solution dried to 97.2%) Solid (>99% purity*)	Visual Visual (25°C) Not stated		**BPR ESPTF, 2002** **BPR Art. 95 dossier, 2014** REACH registration dossier, JS member, Opt-out, 2000
Physical state (appearance) at 20°C and 101.3 kPa	See entry above			
Colour at 20°C and 101.3 kPa	Yellow (92.5% purity, 7.5% water) Yellow (40% aqueous solution dried to 97.2%) Pale yellow (>99% purity*)	Visual Visual (22.8°C) Not stated		**BPR ESPTF, 2002** **BPR Art. 95 dossier, 2014** REACH registration dossier, JS member, Opt-out, 2000
Odour at 20°C and 101.3 kPa	No data			
Melting / freezing point	Decomposition before melting starting at ca 250°C (92.5% purity, 7.5% water)	EEC A.1, OECD 102 (capillary method)		**BPR ESPTF, 2002**

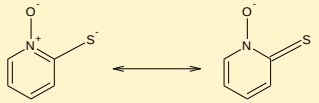
	Decomposition before melting starting at ca 225°C (96.0% purity, 1.5% loss on heating) Decomposition before melting at 236-240°C (>99% purity*)	EEC A.1, OECD 102 (TGA, DSC) EEC A.1, OECD 102 (DSC)		**BPR Art. 95 dossier, 2013a** REACH registration dossier, JS member, Opt-out, 2000
Boiling point at	Not applicable; decomposition before melting (see entry above)			
Relative density	1.60 g/cm^3 at 23.6°C (92.5% purity, 7.5% water) $^{20}_4$D=1.59 (96.0% purity, 1.5% loss on heating) 1.61 g/cm^3 (>99% purity*)	EEC A.3, OECD 109 (gas comparison pycnometer) EEC A.3, OECD 109 (gas comparison pycnometer) EEC A.3, OECD 109 (air comparison pycnometer)		**BPR ESPTF, 2002** **BPR Art 95 dossier,** 2013b REACH registration dossier, JS member, Opt-out, 2000
Granulometry	Mass fraction ≤10 µm: 2.62% (>99% purity*)	Mass based particle size distribution (cascade impaction)	-	REACH registration dossier, JS member, Opt-out, 2000
Vapour pressure	<4.6 x 10^{-5} Pa at 25°C (92.5% purity, 7.5% water) <8.4 x 10^{-7} Pa at 20°C <2.2 x 10^{-6} Pa at 25°C (96.0% purity, 1.5% loss on heating)	EEC A.4 (vapour pressure balance) EEC A.4, OECD 104, OPPTS 830.7950 (isothermal TGA effusion method)	Calculated from a single worst case data point from measurements done at 110-120°C Low reliability of results (low volatility, decomposition occurred within the tested	**BPR ESPTF, 2001** **BPR Art. 95 dossier, 2013c**

	2.1 x 10^{-5} Pa at 25°C (>99% purity*)	EEC A.4, OECD 104 (vapour pressure balance)	temperature range) Extrapolated from measurements done at 180-190°C	REACH registration dossier, JS member, Opt-out, 2000
Henry's law constant	<1.0 x 10^{-8} Pa-m^3/mol	Calculation (vapour pressure/water solubility)	See comments on vapour pressure	**BPR ESPTF, 2002**
	2.14 x 10^{-10} Pa-m^3/mol	Calculation (vapour pressure/water solubility)		**BPR Art. 95 dossier, 2015**
Surface tension	65.0 mN/m at 20.1°C for 1 g/L aqueous solution (92.5% purity, 7.5% water)	EEC A.5, OECD 115 (ring method)		**BPR ESPTF, 2002**
	71.0 mN/m at 20.2°C for 1 g/L sodium pyrithione aqueous solution (40.2% aq. solution)	EEC A.5, OECD 115 (ring method)		**BPR Art. 95 dossier, 2013**
	72.6 mN/m at 20°C for 1 g/L aqueous solution (>99% purity*)	EEC A.5, OECD 115 (ring method)		REACH registration dossier, JS member, Opt-out, 2000
Water solubility at 20 °C	635.8 g/L at 20°C and pH >12 684.1 g/L at 30°C and pH >12 (92.5% purity, 7.5% water)	EEC A.6, OECD 105 (flask-method)	The high pH is due to the alkaline properties of the substance. It is considered technically not feasible to test the solubility at environmentally relevant pH but as the corresponding acid (i.e. pyrithione) has a pKa of 4.7 (see below) the solubility in water might be affected by	**BPR ESPTF, 2002**

	At 10°C, 20°C and 30°C: > 597 g/L in pH 2 buffer (actual pH 7.4) > 590 g/L in pH 5 buffer (actual pH 7.6) > 591 g/L in pH 7 buffer (actual pH 9.3) > 596 g/L in pH 9 buffer (actual pH 9.9) (40% aqueous solution dried to 97.2% purity)	EEC A.6, OECD 105 (flask-method)	low pH. The solutions were not saturated (high viscosity did not allow for further determinations). The buffer capacity of the used buffers was exceeded.	**BPR Art. 95 dossier, 2013**
	58.3-60%w/w at pH 10.5-11 (>99% purity*)	EEC A.6, OECD 105 (flask-method)		REACH registration dossier, JS member, Opt-out, 2000
Partition coefficient (n-octanol/water) and its pH dependency	Log P_{ow}= -2.64 at pH 8.5-8.6 and 20°C (92.5% purity, 7.5% water)	EEC A.8, OECD 107 (shake flask method)	The results might be somewhat uncertain as it is outside the range which is generally applicable to the method. The pH dependency has not been tested and it is not considered required, as the result does not indicate any risk for bioaccumulation. The pKa of the corresponding acid (see below) indicate that the log P_{ow} might be higher at low pH (e.g. pH 5) but log P_{ow} predictions (ACD labs) gives a log P_{ow} of -0.90 for protonated pyrithione (HPT) which does also not indicate	**BPR ESPTF, 2002**

			any concern.	
	Log P_{ow}=< -1.09 at pH 8.0-8.4 and 23°C (40% aqueous solution dried to 95.71% purity)	EEC A.8, OECD 107 (shake flask method)		**BPR Art. 95 dossier, 2013**
	Log P_{ow}=< -2.38 at pH 7 and 20°C (>99% purity*)	EEC A.8, OECD 107 (shake flask method)		REACH registration dossier, JS member, Opt-out, 2000
Thermal stability and identity of breakdown products	Decomposition before melting starting at ca. 250°C (92.5% purity, 7.5% water)	EEC A.1 OECD 102 (capillary method)		**BPR ESPTF, 2002**
	Self-ignition at 240 °C (92.5% purity, 7.5% water)	EEC A.16		**BPR ESPTF, 2002**
	No chemical reaction or transformation was observed below temperatures of 150°C. Decomposition before melting starting at ca 225°C. (96.0% purity, 1.5% loss on heating)	OECD 113 (DSC)		**BPR Art. 95 dossier, 2013a**
	Self-heating/self-ignition at 200°C (96.6% purity)	UN Transport Regulation Class 4, Division 4.2 (VDI 2263 Sheet 1 Grewer-Oven)		BPR Art. 95 dossier, 2016
	Decomposition before melting at 236-240°C (>99% purity*)	EEC A.1, OECD 102 (DSC)		REACH registration dossier, JS member, Opt-out, 2000

	Self-ignition at 230 °C (>99% purity*)	EEC A.16		REACH registration dossier, JS member, Opt-out, 2001
Reactivity towards container material	There have been no recorded observations of reactivity with containers, however because Sodium Pyrithione is normally supplied in aqueous solution, non-protected metal containers are not recommended. Sodium pyrithione is transported and stored in lacquer lines carbon steel drums. [A waiving justification is presented in the BPR Art. 95 dossier for this endpoint.]	-	Justification	**BPR ESPTF** **[BPR Art. 95 dossier]**
Dissociation constant	At 24.4 °C: pK_a=2.2-3.0; mean 2.6 (40.2% aq. solution)	OECD 112, OCSPP 830.7370 (conductometric method)	The quality criteria of OECD 112 not met (the pKa should be replicated within ± 0.1 log units). Sodium pyrithione (NaPT) is the corresponding base of the weak acid "pyrithione" (i.e. HPT). Published data (see e.g. J. Chem Soc., 1960, p 2937-42) indicate a pKa of ~4.7 for HPT which	BPR Art. 95 dossier, 2013

			means that at pH >4.7 the predominant form will be:  The reliability of the experimental data reported by BPR Art. 95 applicant can therefore be questioned.	
Viscosity	Not applicable for the dried substance (i.e. it is a solid).			
Solubility in organic solvents, including effect of temperature on solubility	Not considered relevant. The substance is in ionic form and most likely not soluble in most organic solvents (supported by the log Pow data).			
Stability in organic solvents used in biocidal products and identity of relevant degradation products	Not relevant – it is not used in organic solvents.			

A.1.4. Physical hazards and respective characteristics

Table A.8 Physical hazards and respective characteristics

Hazard class / characteristics	Guideline and Method	Parameter(s)	Results / Waiver	Reference
Explosives	EEC A.14		Not explosive (94.3% purity, 5.7% water).	BPR ESPTF, 2002

Hazard class / characteristics	Guideline and Method	Parameter(s)	Results / Waiver	Reference
	Guidance on the application of the CLP criteria		The substance was screened against the waiving criteria. Since the molecule contains the N-O moiety it did not pass the first criteria. However, the exothermic decomposition energy as determined by DSC was 449 J/g (occurring at 295°C) and thus below 500 J/g. Sodium pyrithione should thus not be classified as an explosive. (dried substance of unknown purity from a 40.8% aqueous solution).	BPR Art. 95 dossier, 2015
			The study does not need to be conducted because there are no chemical groups present in the molecule which are associated with explosive properties in accordance with Column 2, Annex VII of REACH	Reach dossier waiver
Flammable gases			Not applicable- not a gas	
Flammable aerosols			Not applicable- not an aerosol	
Oxidising gases			Not applicable- not a gas	
Gases under pressure			Not applicable- not a gas	
Flammable liquids			Not applicable- not a liquid	
Flammable solids	EEC A.10		Not highly flammable (based on the preliminary test). (92.5% purity, 7.5% water)	BPR ESPTF, 2002
	EEC A.10 UN Test N.1		Not highly flammable (based on the preliminary test). (96.0% purity, 1.5% loss on	BPR Art. 95 dossier, 2013a

Hazard class / characteristics	Guideline and Method	Parameter(s)	Results / Waiver	Reference
			heating)	
	EEC A.10		Not highly flammable (based on the preliminary test). (>99% purity*, 4.3% moisture)	REACH registration dossier, JS member, Opt-out, 2001
Self-reactive substances and mixtures	Guidance on the application of the CLP criteria		[A waiving justification is presented in the BPR Art. 95 dossier for this endpoint.]	[BPR Art. 95 dossier, 2015]
Pyrophoric liquids			Not applicable- not a liquid	
Pyrophoric solids			Not a pyrophoric substance based on the fact that it is tested in air in all studies provided.	
Self-heating substances and mixtures	UN Transport Regulation Class 4, Division 4.2 (VDI 2263 Sheet 1 Grewer-Oven)		Self-heating/self-ignition at 200°C (96.6% purity). DS note: The results may be interpreted as the self-ignition temperature according to EC A.16 (i.e. a sample temperature of 400 °C is reached). The test was done using a 8 cm^3 sample volume and not 1 L as prescribed for the screening test using Grewer-Oven). The full test according to UN test N.4 should have been conducted.	BPR Art. 95 dossier, 2016
Substances and mixtures which in contact with water emit flammable gases			Hazard class not applicable based on the fact that it is placed on the market as an aqueous solution.	
Oxidising liquids			Not applicable- not a liquid	
Oxidising solids	EEC A.17		Not oxidizing (94.3% purity,	BPR ESPTF, 2002

Hazard class / characteristics	Guideline and Method	Parameter(s)	Results / Waiver	Reference
			5.7% water)	
			The study does not need to be conducted because there are no chemical groups present in the molecule which are associated with oxidising properties and hence, the classification procedure does not need to be applied in accordance with Column 2, Annex VII of REACH. DS note: Justification is not in line with waiving criteria in CLP, since the substance contains the N-O-moiety.	Reach dossier waiver
Organic peroxides			Not applicable- not a peroxide	
Corrosive to metals	UN Manual of tests and criteria, 2010 Steel and aluminium plates (3 each) were fully and half-immersed in the solution and exposed in the vapour phase. Test duration 28 days at 55°C. The plates were then evaluated for any corrosion.		No classification is warranted. No corrosion was observed on the aluminium plates even after 4 weeks of exposure. The steel specimens showed localized corrosion already after one week. The attack was the strongest within the first week and for the completely immersed specimens. The localized corrosion depths (12-60 µm) were below the classification criterion (120µm). (40% aqueous solution).	BPR Art. 95 dossier, 2015

Hazard class / characteristics	Guideline and Method	Parameter(s)	Results / Waiver	Reference
			DS note: The equipment used for testing and the volume of solution used is not described. The test was done for an aqueous solution of sodium pyrithione with a specific concentration. It is outlined in the Guidance on application of the CLP criteria that testing of solids that may become liquids (including solutions) may need specific considerations and adaptations of the classification criteria or test protocol. Further testing seems required to conclude on corrosive to metals.	
Auto-ignition temperature (liquids and gases)			Not applicable- not a liquid	
Relative self-ignition temperature for solids	EEC A.16		Self ignition at 240 °C (92.5% purity, 7.5% water)	BPR ESPTF, 2002
	UN Transport Regulation Class 4, Division 4.2 (VDI 2263 Sheet 1 Grewer-Oven)		Self-heating/self-ignition at 200°C (96.6% purity).	BPR Art. 95 dossier, 2016
	EEC A.16		Self ignition at 230 °C (>99% purity*)	REACH registration dossier, JS member, Opt-out, 2001
Dust explosion hazard			No data available – not relevant to the substance as placed on the market (i.e.	

Hazard class / characteristics	Guideline and Method	Parameter(s)	Results / Waiver	Reference
			aqueous solution).	

* The purity of 99% is questioned (i.e. the DS has not access to the study reports). Information in the BPR-dossier states that drying to higher purity than 94% leads to decomposition. In the test on flammability, the purity is claimed as >99% while the moisture content is 4.3% (i.e. water does not appear to be treated as an impurity).

A.1.5. Assessment of physical hazards according to the CLP criteria

A.1.5.1. Assessment of physical hazards

Not relevant for the CLH-dossier.

A.1.5.2. Explosives

Table A.9 Summary table of studies on explosive properties

Method	Results	Remarks	Reference
EEC A.14	Not explosive (94.3% purity, 5.7% water).		BPR ESPTF, 2002
Guidance on the application of the CLP criteria	The substance was screened against the waiving criteria. Since the molecule contains the N-O moiety it did not pass the first criteria. However, the exothermic decomposition energy as determined by DSC was 449 J/g (occurring at 295°C) and thus below 500 J/g. Sodium pyrithione should thus not be classified as an explosive. (dried substance of unknown purity from a 40.8% aqueous solution).		BPR Art. 95 dossier, 2015
	The study does not need to be conducted because there are no chemical groups present in the molecule which are associated with explosive properties in accordance with Column 2, Annex VII of REACH	Waiving argument not valid (see second row)	Reach dossier waiver

A1.5.2.1 Short summary and overall relevance of the provided information on explosive properties
One negative study performed with dried substance in accordance with EEC A.14 is available. In addition two waiving arguments are provided. The substance contains one functional group with potential explosive properties (N-O) which means that the waiving criteria based on structural properties in CLP is not met (i.e. the Reach dossier waiver is not valid). However, since the decomposition energy as determined by DSC is below the trigger no further testing is required.
A1.5.2.2 Comparison with the CLP criteria
The waiving criteria in CLP is met since the decomposition energy was below 500 J/g at the point of decomposition (295°C). It should thus not be classified as an explosive. This is further supported by a negative test according to EEC A.14.
A1.5.2.3 Conclusion on classification and labelling for explosive properties
No classification is proposed (data conclusive but not sufficient for classification).

A.1.5.3. Flammable gases (including chemically unstable gases)

Hazard class not relevant – the substance is not a gas.

Table A.10 Summary table of studies on flammable gases (including chemically unstable gases)
Not relevant.

A1.5.3.1 Short summary and overall relevance of the provided information on flammable gases (including chemically unstable gases)
Not relevant.

A1.5.3.2 Comparison with the CLP criteria
Not relevant.

A1.5.3.3 Conclusion on classification and labelling for flammable gases
Not relevant.

A.1.5.4. Flammable aerosols and aerosols

Hazard class not relevant – the substance is not an aerosol.

Table A.11 Summary table of studies on flammable aerosols and aerosols
Not relevant.

A1.5.4.1 Short summary and overall relevance of the provided information on flammable aerosols and aerosols

A1.5.4.2 Comparison with the CLP criteria
Not relevant.
A1.5.4.3 Conclusion on classification and labelling for flammable aerosols and aerosols
Not relevant.

A.1.5.5. Oxidising gases

Hazard class not relevant – the substance is not a gas.

Table A.12 Summary table of studies on oxidising gases
Not relevant.

A1.5.5.1 Short summary and overall relevance of the provided information on oxidising gases
Not relevant.

A1.5.5.2 Comparison with the CLP criteria
Not relevant.

A1.5.5.3 Conclusion on classification and labelling for oxidising gases
Not relevant.

A.1.5.6. Gases under pressure

Hazard class not relevant – the substance is not a gas.

Table A.13 Summary table of studies on oxidising gases
Not relevant.

A1.5.6.1 Short summary and overall relevance of the provided information on gases under pressure
Not relevant.

A1.5.6.2 Comparison with the CLP criteria
Not relevant.

A1.5.6.3 Conclusion on classification and labelling for gases under pressure
Not relevant.

A.1.5.7. Flammable liquids

Hazard class not relevant – the substance is not a liquid.

Table A.14 Summary table of studies on flammable liquids
Not relevant.

A1.5.7.1 Short summary and overall relevance of the provided information on flammable liquids
Not relevant.
A1.5.7.2 Comparison with the CLP criteria
Not relevant.

A1.5.7.3 Conclusion on classification and labelling for flammable liquids
No relevant.

A.1.5.8. Flammable solids

Table A.15 Summary table of studies on flammable solids

Method	Results	Remarks	Reference
EEC A.10	Not highly flammable (based on the preliminary test). (92.5% purity, 7.5% water)		BPR ESPTF, 2002
EEC A.10 **UN Test N.1**	Not highly flammable (based on the preliminary test). (96.0% purity, 1.5% loss on heating)		BPR Art. 95 dossier, 2013a
EEC A.10	Not highly flammable (based on the preliminary test). (>99% purity*, 4.3% moisture)		REACH registration dossier, JS member, Opt-out, 2001

* The purity of 99% is questioned (i.e. the DS has not access to the study reports). Information in the BPR-dossier states that drying to higher purity than 94% leads to decomposition. In the test on flammability, the purity is claimed as >99% while the moisture content is 4.3% (i.e. water does not appear to be treated as an impurity).

A1.5.8.1 Short summary and overall relevance of the provided information on flammable solids
Three studies performed with dried substance according to EEC A.10 are available. All three studies were negative in the preliminary test i.e. the test material ignited but the flame extinguished within a few seconds after the Bunsen burner was removed.
A1.5.8.2 Comparison with the CLP criteria

Sodium pyrithione should not be classified as a flammable solid under CLP (i.e. the preliminary test of EEC A.10 and the screening test in CLP are principally the same).

A1.5.8.3 Conclusion on classification and labelling for flammable solids
No classification is proposed (data conclusive but not sufficient for classification).

A.1.5.9. Self-reactive substances

Table A.16 Summary table of studies on self-reactivity

Method	Results	Remarks	Reference
Guidance on the application of the CLP criteria	Since the molecule contains a functional group (N-O) which is potentially associated with explosive properties, the SADT was determined. It is stated that as there were no exothermic peaks <150°C (determined by DSC) it could be concluded that the SADT is >75°C meaning that no classification is warranted. (dried substance of unknown purity from a 40.8% aqueous solution).	Tests for SADT should be done in 50 kg packaging according to UN Test H.4 in order to use the waiving criteria. It seems thus that the quoted SADT above cannot be used for waiving.	BPR Art. 95 dossier, 2015

A1.5.9.1 Short summary and overall relevance of the provided information on self-reactive substances
One experimental study relevant to this hazard class is available. The testing strategy used was claimed to be in accordance with the Guidance on the application of the CLP criteria. Since the molecule contains one functional group (N-O) potentially associated with explosive properties, the SADT was claimed to be determined as being >150°C. However, the SADT was based on testing of a small amount of sample using DSC.

A1.5.9.2 Comparison with the CLP criteria
In the study available the SADT is claimed to be >150°C as no exothermic peaks are found below this temperature when assessing a small sample with DSC. According to the Guidance on the application of CLP-criteria, for self-reactive substances the SADT that should be determined to be >75°C for a 50 kg package. Even though it is likely that the SADT would be higher than 75°C for a 50 kg package a full conclusion cannot be drawn.

A1.5.9.3 Conclusion on classification and labelling for self-reactive substances

No classification is proposed (data conclusive but not sufficient for classification).

A.1.5.10. Pyrophoric liquids

Hazard class not relevant – the substance is not a liquid.

Table A.17 Summary table of studies on pyrophoric liquids
Not relevant.

A1.5.10.1 Short summary and overall relevance of the provided information on pyrophoric liquids
Not relevant.

A1.5.10.2 Comparison with the CLP criteria
Not relevant.
A1.5.10.3 Conclusion on classification and labelling for pyrophoric liquids
Not relevant.

A.1.5.11. Pyrophoric solids

Table A.18 Summary table of studies on pyrophoric solids
No data is available.

A1.5.11.1 Short summary and overall relevance of the provided information on pyrophoric solids
No specific data is available. However, based on experience in use it can be concluded that the substance can be safely handled in air (tested in air in all studies available).

A1.5.11.2 Comparison with the CLP criteria
Experience in use shows that the substance is not pyrophoric (i.e. valid waiver according to CLP).

A1.5.11.3 Conclusion on classification and labelling for pyrophoric solids
No classification is proposed (data conclusive but not sufficient for classification).

A.1.5.12. Self-heating substances

Table A.19 Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
UN Transport Regulation Class 4,	Self-heating/self-ignition at 200°C		BPR Art. 95 dossier,

Division 4.2 (VDI 2263 Sheet 1 Grewer-Oven)	(96.6% purity)		2016
EEC A.16	Self ignition at 240 °C (92.5% purity, 7.5% water)		BPR ESPTF, 2002
EEC A.16	Self ignition at 230 °C (>99% purity*)		REACH registration dossier, JS member, Opt-out, 2001

* The purity of 99% is questioned (i.e. the DS has not access to the study reports). Information in the BPR-dossier states that drying to higher purity than 94% leads to decomposition. In the test on flammability, the purity is claimed as >99% while the moisture content is 4.3% (i.e. water does not appear to be treated as an impurity).

A1.5.12.1 Short summary and overall relevance of the provided information on self-heating substances

Three experimental studies conducted with dried substance are available. The first one was conducted using the Grewer-oven whereas the other two was done in accordance with EEC A.16. The studies showed self-ignition temperatures in the range of 200-240°C.

A1.5.12.2 Comparison with the CLP criteria

None of the studies were conducted in accordance with the test method prescribed in CLP (UN test N.4). The Grewer-Oven can be used as a screening test according to the Guidance on the application of the CLP criteria. However, as the first study was conducted using only 8 cm^3 of test substance instead of 1 L as prescribed in the guidance, the result of that study must also be treated as the self-ignition temperature. Thus, the results cannot be fully evaluated against the CLP criteria.

A1.5.12.3 Conclusion on classification and labelling for self-heating substances

No classification proposed (data conclusive but not sufficient for classification).

A.1.5.13. Substances which in contact with water emit flammable gases

Table A.20 Summary table of studies on substances which in contact with water emit flammable gases

No data is available.

A1.5.13.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

No specific data is available. However, based on experience in use (i.e. it is manufactured as an aqueous solution) it can be concluded that the substance does not react with water to emit flammable gases.

A1.5.13.2 Comparison with the CLP criteria

Experience in use shows that the substance does not emit flammable gases in contact with water (i.e. valid waiver according to CLP).

A1.5.13.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases
No classification is proposed (data conclusive but not sufficient for classification).

A.1.5.14. Oxidising liquids

Hazard class not relevant – the substance is not a liquid.

Table A.21 Summary table of studies on oxidising liquids
Not relevant.

A1.5.14.1 Short summary and overall relevance of the provided information on oxidising liquids
Not relevant.

A1.5.14.2 Comparison with the CLP criteria
Not relevant.

A1.5.14.3 Conclusion on classification and labelling for oxidising liquids
Not relevant.

A.1.5.15. Oxidising solids

Table A.22 Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
EEC A.17	Not oxidizing (94.3% purity, 5.7% water).		BPR ESPTF, 2002
	The study does not need to be conducted because there are no chemical groups present in the molecule which are associated with oxidising properties and hence, the classification procedure does not need to be applied in accordance with Column 2, Annex VII of REACH.		Reach dossier waiver

A1.5.15.1 Short summary and overall relevance of the provided information on oxidising solids
One negative study conducted with dried substance in accordance with EEC A.17 is available. The test substance/cellulose mixtures

(10-90%) ignited but the flame extinguished in all cases. In addition one waiving argument is available.

A1.5.15.2 Comparison with the CLP criteria
Since all the test material/cellulose mixtures failed to burn to completion no classification according to CLP is warranted. The waiving argument provided is not valid since the substance contains oxygen, which is not only bonded to carbon or hydrogen (i.e. the N-O moiety).

A1.5.15.3 Conclusion on classification and labelling for oxidising solids
No classification is proposed (data conclusive but not sufficient for classification).

A.1.5.16. Organic peroxides

Hazard class not relevant – the substance is not an organic peroxide.

Table A.23 Summary table of studies on organic peroxides
Not relevant.

A1.5.16.1 Short summary and overall relevance of the provided information on organic peroxides
Not relevant.

A1.5.16.2 Comparison with the CLP criteria
Not relevant.

A1.5.16.3 Conclusion on classification and labelling for organic peroxides
Not relevant.

A.1.5.17. Corrosive to metals

Table A.24 Summary table of studies on the hazard class corrosive to metals

Method	Results	Remarks	Reference
UN Manual of tests and criteria, 2010 Steel and aluminium plates (3 each) were fully and half-immersed in the solution and exposed in the vapour phase. Test duration 28 days at 55°C. The plates were then evaluated for any	No classification is warranted. No corrosion was observed on the aluminium plates even after 4 weeks of exposure. The steel specimens showed localized corrosion already after one week. The attack was the strongest within the first week and	The equipment used for testing and the volume of solution used is not described. The test was done for an aqueous solution of sodium pyrithione with a	BPR Art. 95 dossier, 2015

corrosion.	for the completely immersed specimens. The localized corrosion depths (12-60 µm) were below the classification criterion (120µm). (40% aqueous solution).	specific concentration. It is outlined in the Guidance on application of the CLP criteria that testing of solids that may become liquids (including solutions) may need specific considerations and adaptations of the classification criteria or test protocol.	

A1.5.17.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals
One experimental study conducted with an aqueous solution (40%) is available which is claimed to have been performed in accordance with the UN Manual of tests and criteria. The test plates (steel and aluminium) were fully and half-immersed in the solution and exposed in the vapour phase. Test duration 28 days at 55°C. The plates were then evaluated for any corrosion. The steel plates showed localized corrosion, which depth were below the classification criterion.
A1.5.17.2 Comparison with the CLP criteria
The results indicate that the CLP classification criterion for corrosive to metal is not met. It is noted that the conclusion is valid for the aqueous solution of sodium pyrithione, as placed on the market (40%, pH 9-11). It is not evident whether this conclusion is adequate for all aqueous solutions so that it is general for the inherent properties of dried sodium pyrithione.

A1.5.17.3 Conclusion on classification and labelling for corrosive to metals
No classification is proposed (data conclusive but not sufficient for classification).

A.1.6. Analytical methods for detection and identification

Not applicable for the CLH report.

A.2. Effects against target organisms

Not applicable for the CLH report.

A.3. Assessment of effects on Human Health

A.3.1. Toxicokinetics

Table A.25 Summary table of toxicokinetic studies

Summary table of toxicokinetic studies					
Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results	Remarks (e.g. major deviations)	Reference

Disposition and metabolism via oral and intravenous routes, 18 days, US EPA 85-1, GLP: Yes: Reliability: 1, Key study	Rat, Sprague-Dawley, 10/sex/group	Radiolabelled sodium pyrithione: sodium [pyridine-2,6 ^{14}C]pyrithione (>95% pure) and unlabelled sodium pyrithione (41.41% aqueous solution), Vehicle: p.o. – water; i.v. – 0.9% saline, A: single dose i.v. 0.5 mg/Kg, caudal vein B: single dose p.o. 0.5 mg/Kg C: repeated dose p.o. 0.5 mg/Kg (14 days unlabelled test compound followed by radiolabelled test compound on the fifteenth day) D: single dose p.o. 25 mg/Kg	Based on comparison of urinary and fecal excretion in the i.v. and p.o. dosed groups, it was shown that sodium pyrithione was well absorbed by males and females in all three oral dose groups. Metabolism was extensive. The major urinary metabolite was 2-pyridinethiol-1-oxide-S-glucuronide (designated metabolite K), which is the glucuronic acid conjugate of free pyrithione. Metabolite K represented 59-67% of the dose in 0-72 hour urine after a single 0.5 mg/Kg oral dose, 41-49% after multiple 0.5 mg/Kg oral doses, 50% after a single 0.5 mg/Kg i.v. dose, and 43-47% after a single 25 mg/Kg oral dose. No unconjugated pyrithione was detected. After oral dosing, the concentration of ^{14}C pyrithione equivalents in the blood showed a broad secondary peak after the initial peak following dosing. Evidence of a secondary peak or plateau was also seen after i.v. dosing. Elimination from the blood occurred at several rates, with a slow terminal rate in all of the orally dosed groups.	Metabolite A (7.7 – 21.3% of dose) was not identified.	Doc IIIA A6.2.1/02 Year: 1989 (unpublished)
In vivo skin absorption study, 48 hours, Similar to OECD 427, GLP: Yes,	Rat, Sprague-Dawley, 5 males/group	Sodium [^{14}C]pyrithione – 41.41% sodium pyrithione in aqueous solution with radiochemical purity of >95%,	1.0 mg of sodium pyrithione/kg of bodyweight – 12.5% absorbed 25 mg of sodium pyrithione/kg of bodyweight – 2.5% absorbed	-	Doc IIIA A6.2.1/04 Year: 1989 (unpublished)

Reliability: 2, Key study		Vehicle: none, 1 and 25mg/kg 6 hour exposure time 6, 12, 24, 48 hours sampling time.			
In vitro skin absorption study, OECD 428, GLP: yes, Reliability: 1 Supporting study	Test system: human skin (abdominal) No. of human skin discs per group/from number of different donors: 8/5 in the 341 g/L group and 8/4 in the 0.55 g/L group	Sodium [^{14}C]pyrithione – 40.8% sodium pyrithione in aqueous solution with radiochemical purity of >95% Conc.: 341 g/L and 0.55 g/L Exposure period: 6 hours (non-occlusive)	Absorption values without inclusion of first two tape strips: 341 g/L group: 0.4 ± 0.1% 0.55 g/L group: 3 ± 1%	-	BPR Art. 95 dossier Year: 2014 (unpublished)

Table A.26(a) Toxicokinetic study in rats: Material balance of sodium pyrithione 96 hours after dosing (**Doc IIIA A6.2.1/02**)

		Recovery of radioactivity (mean percent of administered dose ± sd)					
Dose	Sex	Urine	Faeces	Cage wash	Tissues	Carcass	Total
0.5 mg/kg p.o. single dose	M	85.0 ± 2.2	7.0 ± 1.7	1.0 ± 1.8	0.6 ± 0.0	1.5 ± 0.2	95.1 ± 1.7
	F	84.2 ± 2.0	6.0 ± 0.5	0.5 ± 0.4	0.4 ± 0.1	1.3 ± 0.2	92.4 ± 1.9
0.5 mg/kg p.o. multiple doses	M	75.1 ± 2.0	5.3 ± 0.8	2.2 ± 1.0	0.7 ± 0.1	1.7 ± 0.2	85.1 ± 2.4
	F	73.6 ± 4.1	8.0 ± 1.1	2.2 ± 1.1	0.4 ± 0.0	1.3 ± 0.2	85.5 ± 2.7
25 mg/kg p.o. single	M	73.3 ± 1.8	12.3 ± 2.2	0.9 ± 0.3	0.8 ± 0.1	2.1 ± 0.2	89.4 ± 1.1

dose	F	75.7 ± 3.5	11.4 ± 1.9	2.8 ± 1.9	0.6 ± 0.1	1.3 ± 0.3	91.2 ± 1.9
0.5 mg/kg i.v. single dose	M	83.4 ± 1.5	3.2 ± 0.2	1.8 ± 1.0	-	-	88.5 ± 0.7
	F	80.2 ± 4.5	3.2 ± 0.2	4.8 ± 2.2	-	-	88.2 ± 3.3

Table A.26(b) Toxicokinetic study in rats: Distribution of radioactivity in the tissues (**Doc IIIA A6.2.1/02**)

	Mean percentage of the dose 96 hours after dosing					
	0.5 mg/kg p.o. single dose		0.5 mg/kg p.o. multiple dose		25 mg/kg p.o. single dose	
Tissue	M	F	M	F	M	F
Plasma[a]	0.02	0.01	0.02	0.01	0.03	0.02
Blood cells[a]	0.07	0.08	0.06	0.07	0.07	0.07
Liver	0.23	0.14	0.27	0.16	0.29	0.19
Kidney	0.04	0.03	0.06	0.04	0.08	0.03
Heart	0.01	0.01	0.01	0.01	0.01	0.01
Lung	0.01	0.01	0.02	0.01	0.02	0.01
Brain	0.01	0.00	0.01	0.01	0.02	0.01
Fat[a]	0.00	<0.01	0.01	0.00	0.00	<0.01
Skeletal muscle[a]	0.01	0.01	0.01	0.01	0.01	0.01
Spleen	0.01	0.01	0.01	0.01	0.01	0.01
Reproductive organ	0.02	0.00	0.02	0.00	0.03	0.00
Bone Marrow[a]	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Sciatic nerve[a]	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Spinal cord[a]	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Intestines	0.07	0.03	0.09	0.06	0.09	0.07
Intestine contents	0.08	0.05	0.11	<0.01	0.14	0.13
Urinary bladder	0.01	0.01	<0.01	<0.01	<0.01	<0.01
Total	0.60	0.39	0.70	0.39	0.90	0.55

[a] Values for these tissues represent the percentage of the dose in the sample collected for analysis.

Table A.26(c) Toxicokinetic study in rats: Metabolite pattern (**Doc IIIA A6.2.1/02**)

	Percentage of the dose[a] (0 - 72 hour pooled urine)							
	0.5 mg/kg p.o. single dose		0.5 mg/kg p.o. multiple dose		25 mg/kg p.o. single dose		0.5 mg/kg i.v. single dose	
Metabolite	M	F	M	F	M	F	M	F
A	14.7	7.7	21.3	11.0	14.0	14.3	16.2	17.0
D	2.0	3.9	4.5	8.0	5.1	7.3	3.6	2.8
G	2.8	0.4	0.1	0.5	0.2	1.2	0.8	3.0
H	2.6	1.4	2.7	1.4	6.1	1.0	8.0	4.1
K	59.0	67.2	41.4	49.3	43.3	46.8	50.2	49.6
Others[b]	2.8	2.5	3.1	1.7	2.8	2.9	2.3	1.4
Total	83.5	83.1	73.1	72.0	70.8	73.5	81.6	78.2

[a] Mean of duplicate HPLC analyses of pooled urine samples from 5 male or 5 females rats.
[b] Metabolites B, C, E, F, I, J, and L.

Table A.26(d) Results of the *in vivo* skin absorption study (**Doc IIIA A6.2.1/04**)

	^{14}C-NaPT labelled compound					
			% of dose			
Compound applied			100			
Compartments with compound detected			1 mg/kg		25 mg/kg	
1. Protective appliances			1.2±0.5		2.1±1.7	
2. Liquid used for washing the skin			32.7±4.8		13.8±0.7	
3. Skin (with substance not removable, e.g. skin wash, mineralized skin wash, dosed skin, mineralized tap strips)			9.3±3.5		78.1	
4. Blood	Whole blood	plasma	ND	ND	ND	ND
5. Urine			4.8±0.9		1.4±0.2	
6. Faeces			0.8±0.1		0.2±0.1	

7. Removed organs specify organs give sum	Brain Kidneys Liver GI tract Spinal cord	0.00±0.00 0.02±0.01 0.31±013 0.54±0.31 <0.01±0.00	0.0±0.0 0.00±0.01 0.02±0.01 0.22±0.12 0.0±0.0
8. Remaining carcass		0.8±0.2	0.2±0.1
9. Cage rinsing		0.6±0.1	0.1±0.0
Sum of #4 – 9: blood (WBld used), excreta, removed organs, remaining carcass (= absorption)		8.0	2.0
Sum of all detected labelled compound (#1 – 9) (=recovery)		68.3±7.8	77.6±2.3

Table A.26(e) Results of the *in vitro* skin absorption study (BPR Art. 95 dossier, 2014)

Formulation	Undiluted formulation (341 g/L)		Dilution in paint (0.55 g/L)	
Number of human skin discs	8		8	
Number of different donors	5		4	
	Average % RAD[4)]	SD[4)]	Average % RAD	SD
DERMAL ABSORPTION PARAMETERS				
Lag time (h)	1	NA	2	NA
Maximum flux (µg/cm^2/h)	1	2	0.03	0.01
SURFACE COMPARTMENT				
Total skin swabs 6 h	93	3	57	6
Material remaining in donor chamber	0.07	0.05	33	8
Total % non-absorbed[1)]	94	3	90	5
SKIN COMPARTMENT				
Skin	0.08	0.05	0.3	0.2
Tape strips 1&2	0.01	0.005	0.1	0.08
Stratum corneum (tape strips excluding 1&2)	0.04	0.01	0.6	0.3
Total % at dose site (excluding tape strips 1&2)	0.1	0.05	0.9	0.5
RECEPTOR COMPARTMENT				
Receptor fluid (collected over 24 h)	0.3	0.09	2	0.9
Receptor fluid terminal	0.001	0.0004	0.008	0.003
Receptor chamber	0.001	0.0002	0.001	0.001
Total % directly absorbed[2)]	0.3	0.09	2	0.9
OVERALL ABSORPTION				
Total % potentially absorbable (excluding tape strips 1&2)[3)]	0.4	0.1	3	1
Total % recovery	94	3	94	5

RAD = radioactivity, NA = not applicable, SD= Standard deviation

[1)] Total % non-absorbed = % in total skin swabs 6h + % material remaining in donor chamber

[2)] Total % directly absorbed = % receptor fluid + % receptor fluid terminal + % receptor chamber

[3)] Total % potentially absorbable (without tape strips 1&2) = Total % at dose site (excluding tape strips 1&2) + total % directly absorbed

[4)] Average and SD are calculated with data of 6 skins (4 donors), two skin discs were excluded due to low recovery and/or different absorption profile

A3.1.1 Short summary and overall relevance of the provided toxicokinetic information

A GLP study according to US EPA Guideline 85-1 (similar to OECD 417) investigated the disposition and metabolism of sodium pyrithione (NaPT) in rats after oral and intravenous administration (Doc IIIA A6.2.1/02). Based on comparison of urinary and faecal excretion in the i.v. and p.o. dosed groups it was shown that NaPT was well absorbed by males and females in all three oral dose groups. Metabolism was extensive. The major urinary metabolite was 2-pyridinethiol-1-oxide-S-glucuronide (designated metabolite K), which is the glucuronic acid conjugate of free pyrithione. Metabolite K represented 59-67 % of the dose in 0-72 hour urine after a single 0.5 mg/kg oral dose, 41-49 % after multiple 0.5 mg/kg oral doses, 50 % after a single 0.5 mg/kg i.v. dose, and 43-47 % after a single 25 mg/kg oral dose. No unconjugated pyrithione was detected.

After oral dosing, the concentration of ^{14}C pyrithione equivalents in the blood showed a broad secondary peak after the initial peak following dosing. Evidence of a secondary peak or plateau was also seen after i.v. dosing. Elimination from the blood occurred at several rates, with a slow terminal rate in all of the orally dosed groups. No abnormalities were observed in any of the treatment groups.

Another GLP study was performed according to guidelines similar to OECD 427 (Doc IIIA A6.2.1/04). ^{14}C-NaPT (^{14}C at the 2nd and 6th position) in aqueous solution was administered dermally to 2 groups of male rats at 1 or 25 mg/kg, with exposures being of 6 hr. Absorbed and unabsorbed radioactivity was determined at 48 hr after application of labelled NaPT. The extent of systemic absorption of labelled NaPT, determined as the sum of the percentages of ^{14}C-NaPT derived in urine and faeces over 48 hr and in tissues and carcass at 48 hr, was 8% at 1 mg/kg but at 25 mg/kg the fraction absorbed decreased to 2%. However, in the last urine sample the concentration of ^{14}C-NaPT was still increasing, suggesting that some of the compound was leaking from the tissue, probably the skin where 9% was remaining at a 1 mg/kg dose and 1% at 25 mg/kg. It is probably over conservative to consider the whole skin fraction as absorbed; to add half the value is probably more realistic. The dermal absorption should be considered as 12.5% at a 1 mg/kg dose and 2.5% at 25 mg/kg.

Approximately 87% of the total radioactivity excreted in the 0-48 hr fraction was found in the urine. The fraction of the dose excreted in urine and faeces decreased with increased dose. Total recoveries of the radioactivity applied were 68% and 78% for 1 and 25 mg/kg, respectively. The recoveries were low and a probable explanation is that losses of radioactivity occurred during the work-up of the exposed skin samples.

The concentration of ^{14}C-NaPT equivalents in tissues typically was less than 0.05% of the dose with the exception of the liver at 1 mg/kg and intestines at the 1 and 25 mg/kg dose levels (which suggests that ^{14}C-NaPT might have been ingested through preening).

An *in vitro* skin absorption study performed according to the OECD 428 and in accordance with the GLP is also available for sodium pyrithione (BPR Art. 95 dossier, 2014). Sodium pyrithione at concentrations of 341 g/L and 0.55 g/L was exposed for 6 hours under non-occlusive conditions to one group each of 8 human skin discs. The absorption values for sodium pyrithione without inclusion of first two tape strips were found to be 0.4 ± 0.1% for the 341 g/L group and 3 ± 1% for the 0.55 g/L group.

A3.1.2 Values and conclusions used for the risk assessment
Not applicable for the CLH report.

A.3.2. Acute toxicity / STOT SE

A.3.2.1. Acute oral toxicity

Table A.26 Summary table of animal studies on acute oral toxicity

Summary table of animal studies on acute oral toxicity						
Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/group	Test substance (including purity) Vehicle, Dose levels, Type of administration (gavage, in diet, other)	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value LD50	Remarks (e.g. major deviations)	Reference
Acute oral toxicity, OECD 401, GLP: yes, Reliability: 1, Supporting study	Rat, Sprague-Dawley CD, 5 males and 5 females in the 2000 mg/kg dose group 5 females each in the 800 and 1265 mg/kg groups	Sodium pyrithione (40% aqueous solution), Vehicle: none, 800, 1265, and 2000 mg/kg bw 14 days post exposure period, Oral gavage	↑ mortality: 0, 3 and 5 animals died in the 800, 1265 and 2000 mg/kg groups, respectively. ↑ clinical signs: ataxia, hunched posture, lethargy, decreased respiratory rate and laboured respiration, ptosis were noted in all dosed groups. Piloerection and loss of righting reflex were noted in all animals in the 1265 or 2000 mg/kg groups. ↑ pathology: haemorrhagic or abnormally red lungs, dark liver or patchy pallor of the liver, dark kidneys and haemorrhage of the gastric mucosa, slight haemorrhage of the small intestine.	Females: 1208 mg/kg bw	-	Doc IIIA A6.1.1/01, Year: 1996 (unpublished)
Acute oral	Rat,	Sodium pyrithione	↑ mortality	1100	-	Doc IIIA

toxicity, US EPA 81-1, GLP: yes, Reliability: 1, Supporting study	Wistar albino, 5/sex/group	(43.76% aqueous solution), Vehicle: none, 1000, 1100, 1200, 1500, 1900, 2000, and 2500 mg/kg bw, 14 days post exposure period Oral gavage	↑ clinical signs: ataxia, lethargy, tremors, diarrhoea, prostration, ptosis, flaccid muscle tone, bloated abdomen, piloerection, chromorhinorrhea, convulsion, brown staining of body areas, wetness of the anogenital area and ocular discharge. One female dosed at 1,100 mg/kg exhibited apparent paralysis of the fore limbs. ↑ pathology: haemorrhagic or abnormally red lungs, dark liver or patchy pallor of the liver, dark kidneys and haemorrhage of the gastric mucosa. Surviving animals recovered 3 to 8 days after dosing.	mg/kg bw		A6.1.1/02, Year: 1987 (unpublished)
Acute oral toxicity (acute toxic class method), OECD 423, GLP: yes, Reliability: 1, Key study	Rat, Wistar Crl:WI (Han), 3 females/group	Sodium pyrithione (40.8% aqueous solution), Vehicle: none, 300 and 816 mg/kg bw 14 days post exposure period Oral gavage	↑ mortality: Two females in the 816 mg/kg group were found dead on Day 2. ↑ clinical signs: lethargy, hunched posture, piloerection and ptosis (300 and 816 mg/kg); uncoordinated movements (300 mg/kg only) and restless behaviour (816 mg/kg only). The symptoms recovered by Days 4 and 6, except hunched posture and piloerection for one animal at 300 mg/kg that lasted until Days 7 and 10. ↑ pathology: The surviving animal at 816 mg/kg had macroscopic findings in stomach, liver and pancreas grown together with the	Between 300 and 816 mg/kg bw	-	BPR Art. 95 dossier Year: 2014 (unpublished)

			diaphragm. No findings in the animals that died before scheduled necropsy. Irregular surface of the stomach, enlarged spleen and thickened wall of the pylorus was observed at 300 mg/kg.			
Acute oral toxicity (acute toxic class method), OECD 423, GLP: yes, Reliability: 1, Supporting study	Rat, Sprague-Dawley, 3 males and 3 females (200 mg/kg); 3 females (2000 mg/kg)	Sodium pyrithione (>95%), Vehicle: water, 200 and 2000 mg/kg bw 14 days post exposure period Oral gavage	Mortality: "No deaths were noted at 200 mg/kg. All animals treated at 2000 mg/kg were found dead one hour after dosing." Clinical signs: "hunched posture was noted in all animals. Lethargy was noted in males treated with 200 mg/kg and females treated at 2000 mg/kg. Occasional body tremors and increased lachrymation were observed at 2000 mg/kg. Animals treated at 200 mg/kg showed recovery 1 to 2 days after dosing." Pathology: "Gross findings in animals receiving 2000 mg/kg that died during the study included haemorrhagic lungs, dark liver, dark kidneys, pale yellow liquid present in the stomach, severe haemorrhage of the gastric mucosa and slight haemorrhage of the small intestine. No abnormalities were noted in animals that received 200 mg/kg surviving to the end of the observation period."	Between 200 and 2000 mg/kg bw	The DS does not have access to the full study report.	REACH registration dossier, JS member, Opt-out Year: 2002

Table A.27(a) Details of the acute oral toxicity study (**Doc IIIA A6.1.1/01**)

Dose [mg active ingredient /kg]	Number of dead / number of investigated	Time of death (range)	Observations	Macroscopic Observations
800	0/5	n.a.	ataxia, decreased respiratory rate, hunched posture, laboured respiration, lethargy, splayed gait	none
1265	3/5	day of dosing - 1 day	ataxia, decreased respiratory rate, hunched posture, laboured respiration, lethargy, pilo-erection, ptosis, tonic and clonic convulsions	lungs: haemorrhagic liver: dark kidneys: dark non-glandular epithelium of the stomach: scattered white foci
2000 (female)	5/5	1 day - 2 days	ataxia, decreased respiratory rate, hunched posture, laboured respiration, lethargy, pilo-erection, ptosis	lungs: haemorrhagic, abnormally red liver: dark, patchy pallor kidneys: dark gastric mucosa: haemorrhagic small intestine: haemorrhagic, slight
2000 (male)	4/5	day of dosing - 2 days	ataxia, decreased respiratory rate, hunched posture, laboured respiration, lethargy, pilo-erection, ptosis	lungs: haemorrhagic, abnormally red liver: dark, patchy pallor kidneys: dark gastric mucosa: haemorrhagic small intestine: haemorrhagic, slight
LD_{50} value	females: 1208 mg active ingredient/kg body weight			

Table A.27(b) Details of the acute oral toxicity study (**Doc IIIA A6.1.1/02**)

Dose [mg 40% Sodium Omadine /kg]	Number of dead males /females	Time of death (range)	Observations	Macroscopic Observations
1000	0/2	1 day after dosing.	lethargy, ptosis, prostration, ataxia, diarrhea, brown staining of the nose/mouth and anogenital area, and alopecia at anogenital area.	Congested lungs, lungs hemorrhagic, liver mottled, red areas in stomach and intestinal areas, intestines distended with mucus
1100	0/1	2 day after dosing	lethargy, ptosis, prostration, ataxia, diarrhea, brown staining of the nose/mouth and anogenital area, and alopecia at anogenital area.	Congested lungs, intestines distended with yellow mucus
1200	1/3	1 female at day of dosing and 2 females at day 1; 1 male at day 7	lethargy, ptosis, prostration, ataxia, diarrhea, brown staining of the nose/mouth and anogenital area, and alopecia at anogenital area.	Congested lungs, lungs hemorrhagic, liver mottled, pale spleen, red areas in stomach and intestinal areas, intestines distended with mucus
1500	0/5	4 animals on day of dosing and 1 animal on 1 day after dosing	lethargy, ptosis, prostration, ataxia, diarrhea, brown staining of the nose/mouth and anogenital area, and alopecia at anogenital area.	Congested lungs, lungs hemorrhagic, liver mottled, spleen darker than normal, red areas in stomach and intestinal areas, intestines distended with mucus
1900 (males only)	1	Day of dosing	lethargy, ptosis, prostration, ataxia, diarrhea, brown staining of the nose/mouth and anogenital area, and alopecia at anogenital area.	Congested lungs, lungs hemorrhagic, liver mottled, red areas in stomach and intestinal areas, intestines distended with mucus

Dose [mg 40% Sodium Omadine /kg]	Number of dead males /females	Time of death (range)	Observations	Macroscopic Observations
2000 (males only)	3	Day of dosing	lethargy, ptosis, prostration, ataxia, diarrhea, brown staining of the nose/mouth and anogenital area, and alopecia at anogenital area.	Congested lungs, lungs hemorrhagic, liver mottled, red areas in stomach and intestinal areas, intestines distended with mucus
2500 (males only)	5	Day of dosing	lethargy, ptosis, prostration, ataxia, diarrhea, brown staining of the nose/mouth and anogenital area, and alopecia at anogenital area.	Congested lungs, lungs hemorrhagic, liver mottled, spleen darker than normal, red areas in stomach and intestinal areas, intestines distended with mucus
LD_{50} value	females: 1100 mg males: 2000 mg Males & Females Combined: 1500 mg			

Table A.27 Summary table of human data on acute oral toxicity
No human data is available.

Table A.28 Summary table of other studies relevant for acute oral toxicity
No further relevant studies.

A3.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity
The acute oral toxicity of sodium pyrithione has been investigated in four rat studies. In all the studies signs of systemic toxicity were noted in all dosed groups and mortality was noted during the day of dosing and up to 7 days after dosing. Surviving animals recovered 3 to 8 days after dosing except in one case where hunched posture and piloerection lasted until 7 to 10 days.

A3.2.1.2 Comparison with the CLP criteria
Classification for acute oral toxicity under the CLP Regulation is required for substances with an acute oral LD50 value of ≤ 2000 mg/kg bw. Category 4 is assigned for substances with LD50 value > 300 and ≤ 2000 mg/kg bw. Category 3 is assigned when LD50 value is > 50 and ≤ 300 mg/kg bw.

In the four available studies the LD50 values of sodium pyrithione were 1208, 1100, between 300 and 816, and between 200 and 2000 mg/kg bw. In the third study, there were no deaths at 300 mg/kg. Therefore, the first three studies clearly suggest Category 4 for sodium pyrithione. In the fourth study there were no deaths at 200 mg/kg and minimal systemic toxicity (hunched posture, lethargy) that was recovered within 2 days. Overall, the four studies indicates that sodium pyrithione should be classified under Category 4. The relevant LD50 value is in the range of 300 – 816 mg/kg bw.

The DS proposes an oral ATE vlaue of 500 mg/kg bw for the classification of mixtures containing sodium pyrithione. The proposed oral ATE value for sodium pyrithione is the converted acute toxicity point estimate according to the Table 3.1.2 of Annex I to the CLP Regulation.

A3.2.1.3 Conclusion on classification and labelling for acute oral toxicity
Based on the available studies, the DS proposes Category 4 for acute oral toxicity for sodium pyrithione according to the CLP criteria. The corresponding hazard statement is H302: Harmful if swallowed.

The DS proposes an oral ATE value of 500 mg/kg bw for the classification of mixtures containing sodium pyrithione.

A3.2.1.4 Conclusion on acute oral toxicity related to risk assessment
Not applicable for the CLH report.

A.3.2.2. Acute dermal toxicity

Table A.29 Summary table of animal studies on acute dermal toxicity

Summary table of animal studies on acute dermal toxicity						
Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/group	Test substance (including purity), Vehicle, Dose levels, Surface area,	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value LD50	Remarks (e.g. major deviations)	Reference
Acute dermal toxicity study, OECD 402, GLP: yes, Reliability: 1,	Rat, Sprague-Dawley, Male and female, 5/sex/group	Sodium pyrithione (< 95%), Vehicle: none, 2000 mg/kg, Area covered: 10% of body surface, Exposure: 24 hours semi-occluded	No mortality or abnormality at necropsy. Local toxic effects of (eschar formation) were observed.	>2000 mg/kg bw	-	Doc IIIA A6.1.2/01 Year: 2001 (unpublished)

Supporting study		dermal application, Post-exposure period: 14 days				
Acute dermal toxicity study, US EPA FIFRA 81-2, GLP: yes, Reliability: 1, Key study	Rabbit, New Zealand albino, Male and female, 5/sex/group	Sodium pyrithione (43.78% aqueous solution), Vehicle: none, 1500, 1650, 1800, and 2000 mg/kg, Area covered: 10% of body surface, Exposure: 24 hours occlusive dermal application, Post-exposure period: 14 days	↑ mortality ↑ clinical signs: emaciation, few feces, ptosis, unkempt appearance, diarrhea, alopecia, ataxia, bloated abdomen, soiling of the anogenital area, pupilary dilation, wetness and yellow staining of the fore limbs, yellow nasal discharge, and alopecia. ↑ pathology: abnormalities of the lungs, liver, gall bladder, spleen, gastrointestinal tract, kidneys, urinary bladder, brown and red staining of the nose/mouth area, red coloration of the body wall and fat, excessive fluid in the peritoneal cavity and at the site of the treated skin.	1800 mg/kg bw	-	Doc IIIA A6.1.2/02 Year: 1987 (unpublished)
Acute dermal toxicity study, OECD 402, GLP: yes, Reliability: 1, Supporting study	Rat, Wistar Crl:WI (Han), Male and female, 5/sex/group	Sodium pyrithione (40.8% aqueous solution), Vehicle: none, 2000 mg/kg, Area covered: 10% of body surface, Exposure: 24 hours dermal application, Post-exposure period: 14 days	↑ mortality: one male and one female were dead on Day 2 ↑ clinical signs: lethargy, tremor, erythema focal, necrosis, scars, scales, scabs, thickened area, chromodacryorrhoea, hypothermia, flat posture, hunched posture, uncoordinated movements, slow breathing, piloerection and ptosis were observed among the animals. ↑ pathology: dark red foci on the stomach glandular mucosa and reddish clear fluid in the thoracic and abdominal cavities were noted in the dead animals. The pathology of the sacrificed animals was normal.	> 2000 mg/kg bw	-	BPR Art. 95 dossier, Year: 2013 (unpublished)

Table A.30(a) Details of the dermal acute toxicity study (**Doc IIIA A6.1.2/01**)

Dose [mg/kg]	Number of dead / number of investigated	Time of death (range)	Observations		
			systemic	local	post mortem
2000	0/5 (males)	n.a.	chromodacryorrhoea	erythema, eschar formation	none
2000	0/5 (females)	n.a.	chromodacryorrhoea	eschar formation	none
LD_{50} value	> 2000 mg/kg				

Table A.30(b) Details of the dermal acute toxicity study (**Doc IIIA A6.1.2/02**)

Dose [mg/kg]	Number of dead males/females	Time of death (range)	Observations		
			systemic	local	post mortem
1500	1/2	Day 1	Yellow nasal discharge, lethargy, emaciation, ptosis, diarrhea, alopecia, ataxia, and body weight loss	Skin irritation at site of application	Abnormalities in lungs, kidneys, gastronintestinal tract
1650	1/3	Days 1-4	Yellow nasal discharge, lethargy, emaciation, ptosis, diarrhea, alopecia, ataxia, and body weight loss	Skin irritation at site of application	Abnormalities in lungs, kidneys, gastronintestinal tract

Dose [mg/kg]	Number of dead males/females	Time of death (range)	Observations		
			systemic	local	post mortem
1800	2/2	Day 1	Yellow nasal discharge, lethargy, emaciation, ptosis, diarrhea, alopecia, ataxia, bloated abdomen, and body weight loss	Skin irritation at site of application	Abnormalities in lungs, kidneys, gastronintestinal tract, gall bladder, spleen, excess fluid in peritoneal cavity, red coloration of the body wall
2000	3/4	Day 1-2	Yellow nasal discharge, lethargy, emaciation, ptosis, diarrhea, alopecia, ataxia, bloated abdoment, and body weight loss	Skin irritation at site of application	Abnormalities in lungs, kidneys, gastronintestinal , tract gall bladder, spleen, excess fluid in peritoneal cavity, red coloration of the body wall
LD_{50} value	Males & Females Combined : 1800 mg/kg bw (1600 – 2000 mg/kg)				

Table A.30 Summary table of human data on acute dermal toxicity
No human data is available.

Table A.31 Summary table of other studies relevant for acute dermal toxicity
No further relevant studies.

A3.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity
The acute dermal toxicity of sodium pyrithione has been investigated in two rat and one rabbit studies. In one rat study there were no mortalities or systemic effects and in the other rat study only two animals died while clinical signs were note in all animals but macroscopic findings only in the dead ones. In both the rat studies the LD50 value was > 2000 mg/kg bw. In the rabbit study however there were clinical signs, macroscopic findings, and increased mortality (male/female per 5 animals): 1/2, 1/3, 2/2 and 3/4 at 1500,

1650, 1800 and 2000 mg/kg groups. The LD50 value for males & female combined was 1800 mg/kg bw.

A3.2.2.2 Comparison with the CLP criteria
Classification for acute dermal toxicity under the CLP Regulation is required for substances with an acute dermal LD50 value of ≤ 2000 mg/kg bw. Category 4 is assigned for substances with LD50 value > 1000 and ≤ 2000 mg/kg bw.

The lowest LD50 value for sodium pyrithione is 1800 mg/kg bw from a reliable study. Therefore, sodium pyrithione should be classified under Category 4.

A3.2.2.3 Conclusion on classification and labelling for acute dermal toxicity
Based on the available studies, the DS proposes Category 4 for acute dermal toxicity for sodium pyrithione according to the CLP criteria. The corresponding hazard statement is H312: Harmful in contact with skin.

The dermal ATE value for sodium pyrithione is 1800 mg/kg bw.

A3.2.2.4 Conclusion on acute dermal toxicity related to risk assessment
Not applicable for the CLH report.

A.3.2.3. Acute inhalation toxicity

Table A.32 Summary table of animal studies on acute inhalation toxicity

Summary table of animal studies on acute inhalation toxicity						
Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/group	Test substance (including purity), form (gas, vapour, dust, mist) and particle size (MMAD) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value LC50	Remarks (e.g. major deviations)	Reference
Acute inhalation toxicity study,	Rat, Sprague-Dawley, Male and female,	Sodium pyrithione (43.78% aqueous solution), Mist, MMAD: 2.3 – 3.2 µm	↑ mortality at all of the exposure levels ↑ clinical signs: laboured breathing, at all exposure levels, ↑ impaired hind limb, ↑ pulmonary congestion.	1.08 mg/l	-	Doc IIIA A6.1.3/01 Year: 1987

US EPA 81-3, GLP: yes, Reliability: 2 (since it was whole-body exposure), Supporting study	5/sex/group	Nominal conc.: 6.6, 8.1, 18.6, 23.7, and 25.9 mg/L, Analytical conc.: 0.14, 0.58, 0.79, 0.95, and 1.4 mg/L, Whole-body, Duration: 4 hour	↓ bw gain (due to high mortality at the higher dose levels, body weight effects could only be assessed at the two lowest doses)			(unpublished)
Acute inhalation toxicity study, OECD 403, GLP: yes, Reliability: 1, Key study	Rat, Wistar Crl:WI(Han), Male and female, 5/sex in 1 mg/l group and 5 females in 0.5 mg/l group	Sodium pyrithione (40.8% aqueous solution), Mist, MMAD: 1.9 – 2.1 µm Nose-only, Duration: 4 hour, Exposure levels: 0.5 and 1 mg/l Nominal conc.: 1.15 and 1.4 mg/l Analytical conc.: 0.5 and 1.1 mg, Nose-only, Duration: 4 hour	↑ mortality: at 1 mg/l all 5 females were killed in extremis between Days 11 and 12. No mortality occurred in males. ↑ clinical signs: at 1 mg/l – lethargy, hunched posture (through the observation period only for females), slow breathing, piloerection, chomodacryorrhoea and/or ptosis between Days 1 and 7 (in males) and Days 1 and 3 (in females) post-exposure. Between Day 8 and 12 the females showed tremors, flat posture, abnormal gait, paralyses of the hind legs, chomodacryorrhoea, maculate erythema of the tail piloerection and/or a lean appearance. At 0.5 mg/l – slow breathing during exposure; hunched posture and abnormal gait in one female on Day 10 post-exposure. ↑ pathology: The females killed in extremis showed emaciation (all three), abnormalities of the thymus (reduced in size in one animal) and adrenal glands (enlarged in one animal).	Between 0.5 – 1 mg/l	-	BPR Art. 95 dossier Year: 2014 (unpublished)

			Body weight loss was noted in all surviving animals during the first week post-exposure. All males in the 1 mg/l group and one female (of 0.5 mg/l group) regained weight during the second week. The body weights of remaining four females in the 0.5 mg/l group declined during the second week.			

Table A.33(a) Details of the inhalation acute toxicity study (**Doc IIIA A6.1.3/01**)

Dose [mg/L]	Number of dead/number of investigated	Time of death (range)	Observations	Macroscopic Observations
1.4	M – 3/5 F – 3/5	Day 10-13 Day 12	Increased salivation during and immediately after exposure. Post exposure – lethargy, irregular breathing, material around nose, material around eye, prostration, body surface stained	Lungs: both appeared bright red in color. Intestines: containing excessive fluid from transparent to yellow in color. Bladder: excessive fluid with one animal having dark fluid.
0.95	M – 0/5 F – 1/5	Day 14 found dead	Increased salivation during and immediately after exposure. Staining observed around the nose and on the body and alopecia. Impaired hind limb only after day 10.	Lungs: Only one animal was observed to have both lungs colored bright red. Intestines: containing a clear yellow fluid to a dark viscous fluid

Dose [mg/L]	Number of dead/number of investigated	Time of death (range)	Observations	Macroscopic Observations
0.79	M – 3/5 F – 5/5	Day 12 – 14 Day 12 - 14	Increased salivation during and immediately after exposure. Lethargy, irregular breathing, staining around nose and eyes and on the body surface. Impaired hind limb only after day 10.	Lungs: both appeared bright red in color. Intestines: containing excessive fluid from transparent to yellow in color. Bladder: excessive fluid with one animal having dark fluid.
0.58	M – 0/5 F – 2/5	Days 10 & 11	Increased salivation during and immediately after exposure. Staining around nose, eyes and on the body surface. Impaired hind limb only in female animals.	Intestines: containing excessive fluid from transparent to yellow in color.
0.14	M – 0/5 F – 0/5	On day 14 one female found dead just prior to sacrifice	Increased salivation during and immediately after exposure. Lethargy, prostration, and Staining around nose, eyes and on the body surface. These observations were only observed in a few animals.	No visible abnormalities
LC_{50} value	males + females: 1.08 mg/L (95% confidence limits = 0.71 – 1.66 mg/L)			

Table A.33 Summary table of human data on acute inhalation toxicity

No human data is available.

Table A.34 Summary table of other studies relevant for acute inhalation toxicity
No further relevant studies available.

A3.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity
Two acute inhalation toxicity studies are available for sodium pyrithione, one with the Sprague-Dawley rats and the other with Wistar rats.
The study with Sprague-Dawley rats (Doc IIIA A6.1.3/01) was performed with whole-body exposure which makes it likely that an unknown amount of test substance had been ingested by preening and impaired hind limb suggesting oral intake (even if it cannot be excluded that the hind limb effect is not due to a systemic effect after inhalation). Mortality was seen at all of the exposure levels, with most of the deaths occurring on the first day post-dose. Toxicologically significant pharmacotoxic signs, such as laboured breathing, were noted at all exposure levels. Due to high mortality at the higher dose levels, body weight effects could only be assessed at the two lowest doses. Weight gain was depressed at both doses during the two-week post-exposure period. Pulmonary congestion was the most common macroscopic observation at necropsy. No gross pulmonary abnormalities were seen in animals that survived the observation period.

The study with Wistar rats (BPR Art. 95 dossier, 2014) was performed with nose-only exposure at two dose groups (0.5 and 1 mg/l). All 5 females in 1 mg/l group were killed between Days 11 and 12 while no mortality was seen in males. Clinical signs in the 1 mg/l group included lethargy, hunched posture, slow breathing, piloerection, chomodacryorrhoea and/or ptosis. Macroscopic findings in this group included emaciation, abnormalities of the thymus and adrenals. In the 0.5 mg/l group all the animals had slow breathing, and only one had hunched posture and abnormal gait on Day 10 only. There were no macroscopic findings in this group. Body weight loss was noted in all surviving animals during the first week post-exposure. All males in the 1 mg/l group and one female (of 0.5 mg/l group) regained weight during the second week. The body weights of remaining four females in the 0.5 mg/l group declined during the second week.

A3.2.3.2 Comparison with the CLP criteria
Classification for acute inhalation toxicity under the CLP Regulation is required for substances with an acute inhalation LC50 value (dusts and mists) of ≤ 5 mg/L. Category 4 is assigned for substances with LC50 value > 1 and ≤ 5 mg/L. Category 3 is assigned for substances with LC50 value > 0.5 and ≤ 1 mg/L.

In the study with Sprague-Dawley rats the LC50 value was 1.08 mg/L. However, in the study with Wistar rats the LC50 value was in the range of 0.5 – 1 mg/L. Therefore, sodium pyrithione should be classified under Category 3.

The DS proposes an inhalation ATE value of 0.5 mg/L (dusts and mists) for the classification of mixtures containing sodium pyrithione. The proposed inhalation ATE value for sodium pyrithione is the converted acute toxicity point estimate according to the Table 3.1.2 of Annex I to the CLP Regulation.

A3.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity
Based on the available studies, the DS proposes Category 3 for acute inhalation toxicity for sodium pyrithione according to the CLP criteria. The corresponding hazard statement is H331: Toxic if inhaled.

The DS proposes an inhalation ATE value of 0.5 mg/L (dusts and mists) for the classification of mixtures containing sodium pyrithione.

A3.2.3.4 Conclusion on acute inhalation toxicity related to risk assessment
Not applicable for the CLH report.

A.3.2.4. Specific target organ toxicity – single exposure Category 1 and 2 (STOT SE 1 and 2)

Table A.35 Summary table of animal studies on Specific Target Organ Toxicity STOT SE 1 and 2
The standard animal studies that provide this information are acute toxicity studies which are summarised in tables 27, 30 and 33 above and are thus not repeated here.

Table A.36 Summary table of human data on Specific Target Organ Toxicity STOT SE 1 or 2
No human data is available.

Table A.37 Summary table of other studies relevant for Specific Target Organ Toxicity STOT SE 1 and 2
No further relevant studies.

A3.2.4.1 Short summary and overall relevance of the provided information on STOT SE 1 and 2
The clinical signs of toxicity observed in the acute toxicity studies with sodium pyrithione appear to be non-specific toxic effects. No specific target organ toxicity was observed in these studies at non-lethal doses.

A3.2.4.2 Comparison with the CLP criteria
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).

There were no significant and/or severe toxic effects observed for sodium pyrithione that are indicative of STOT SE 1 or 2 classification.

A3.2.4.3 Conclusion on classification and labelling for STOT SE 1 and 2
Based on the available data, the DS proposes no classification for STOT SE 1 or 2 for sodium pyrithione according to the CLP criteria.

A.3.2.5. Specific target organ toxicity – single exposure Category 3 (STOT SE 3)

Table A.38 Summary table of animal studies on STOT SE 3
The standard animal studies that could provide this information are acute toxicity studies which are summarised in tables 27, 30 and 33 above and are thus not repeated here.

Table A.39 Summary table of human data on STOT SE 3
No relevant human data available.

Table A.40 Summary table of other studies relevant for STOT SE 3
No further relevant studies.

A3.2.5.1 Short summary and overall relevance of the provided information on STOT SE 3
The only clinical signs of toxicity reflective of respiratory tract irritant effects observed at non-lethal doses was slow breathing during the exposure of sodium pyrithione in an acute inhalation toxicity study. Clinical signs of narcotic effects such as ataxia and lethargy were observed in acute toxicity studies with sodium pyrithione however these could have been caused by general distress of the animals.

A3.2.5.2 Comparison with the CLP criteria
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 sodium pyrithione that are indicative of STOT SE 3 classification.

A3.2.5.3 Conclusion on classification and labelling for STOT SE 3
Based on the available studies, the DS proposes no classification for STOT SE 3 for sodium pyrithione according to the CLP criteria.

A3.2.5.4 Overall conclusion on acute toxicity related to risk assessment
Not applicable for the CLH report.

A.3.3. Skin corrosion and irritation

Table A.41 Summary table of in vitro studies on skin corrosion/irritation

Summary table of in vitro studies on skin corrosion/irritation					
Method, Guideline, GLP status, Reliability, Key/supportive study	Test substance (including purity), Vehicle, Doses	Relevant information about the study	Results	Remarks (e.g. major deviations)	Reference
Reconstructed Human Epidermis Test Method, OECD 439, GLP: yes, Reliability: 1, Supporting study	Sodium pyrithione (40.8% aqueous solution), Vehicle: none 3 tissues per treatment with test substance together with negative and positive controls with 25 µl each. (In addition 3 killed tissues treated with test substance and 3 killed non-treated tissues were used for the cytotoxicity evaluation with MTT as sodium pyrithione was found to interact with MTT).	Test system: EPISKIN Small Model™. Negative control: Phosphate buffered saline Positive control: 5% (aq) sodium dodecyl sulphate Exposure period: 15 minutes Post-treatment incubation period: 42 hours.	Non-irritant. The relative mean tissue viability compared to negative controls was 114%.	The non-specific reduction of MTT by sodium pyrithione was 0.11% of the negative controls. The net OD of the treated killed tissues was subtracted from the ODs of the test substance treated viable tissues.	BPR Art. 95 dossier Year: 2014 (unpublished)

Table A.42(a) Results of *in vitro* skin irritation test: mean absorption and mean tissue viability (BPR Art. 95 dossier, 2014)

	A (OD_{570})	B (OD_{570})	C (OD_{570})	Mean (OD_{570}) ± SD	Mean tissue viability (percentage of control)
Negative control	0.988	1.019	1.102	1.036 ± 0.059	100
Sodium pyrithione	1.183	1.147	1.203	1.178 ± 0.029	114
Positive control	0.045	0.079	0.102	0.075 ± 0.029	7

Table A.42 Summary table of animal studies on skin corrosion/irritation

Summary table of animal studies on skin corrosion/irritation					
Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/group	Test substance (including purity), Vehicle, Dose levels Duration of exposure	Results Average score for erythema/eschar and oedema (24, 48, 72 h) per animal, observations and time point of onset, reversibility, other adverse local/systemic effects, histopathological findings	Remarks (e.g. major deviations)	Reference
Acute Dermal Irritation/Corrosion Study, 14 days, OECD 404, GLP: yes, Reliability: 1, Key study	Rabbit, New Zealand White, 3 females	Sodium pyrithione powder (purity: <95%), Vehicle: none Total mass applied: 0.5 gram Duration of exposure: 4 hours	Erythema/eschar: In 2/3 animals severe erythema were noted. Eschar was formed subsequently but finally desquamated and skin was normal again at the end of the observation period. Oedema: In all animals oedema were noted already after the patch removal. Whereas 1/3 animals was free from oedema from 24 h p.a. onwards, oedema in different grades of severity were noted in the other two animals until 6 or 10 days p.a. Skin lesions at the application sites were reversible within 14 days p.a.	-	Doc IIIA A6.1.4/01 Year: 2001 (unpublished)

Acute Dermal Irritation/Corrosion Study, 72 hours, Similar to OECD 404, GLP: yes, Reliability: 1, Supporting study	Rabbit, New Zealand Albino, 6 animals	Sodium pyrithione (43.7% aqueous solution), Vehicle: none Total mass applied: 0.5 gram Duration of exposure: 4 hours	Erythema: Erythema was absent to slight at 4.5 - 5, 24, 48, and 72 hours Oedema: Oedema was absent to slight at 4.5 - 5, 24, 48, and 72 hours	-	Doc IIIA A6.1.4/02 Year: 1987 (unpublished)
Acute Dermal Irritation/Corrosion Study, 72 hours, OECD 404, GLP: yes, Reliability: 1, Key study	Rabbit, New Zealand White, 3 males	Sodium pyrithione powder (purity: >95%), Vehicle: water Total mass applied: 0.5 gram Duration of exposure: 4 hours	Erythema: Slight erythema was noted in 2 animals at 24 hours. Oedema: Slight oedema was noted in 1 animal at 1 and 24 hours	-	BPR Art. 95 dossier Year: 2014 (unpublished)
Acute Dermal Irritation/Corrosion Study, 72 hours, OECD 404, GLP: yes,	Rabbit, New Zealand White, 3 females	Sodium pyrithione, Vehicle: water Total mass applied: 0.5 gram	"Well define erythema and slight oedema were noted in all treated skin sites at the 1 hour observation period with well define erythema and very slight oedema at the 24 hour observation. Very slight erythema was noted at all treatment sites at the 48 hour observation. All treated skin sites appeared normal at the 72 hour observation period. The findings for the three animals at each timepoint were the same."	The DS does not have access to the full study report.	REACH registration dossier, JS member, Opt-out Year: 2000

Reliability: 1, Key study		Duration of exposure: 4 hours			

Table A.43(a) Results of the acute dermal irritation/corrosion study in rabbits (**Doc IIIA A6.1.4/01**)

Time after the end of the exposure	Erythema / Eschar animal Nos.			Oedema animal Nos.		
	1	2	3	1	2	3
1 h	0	1[d]	1	1	4	1
24 h	0	2[d]	1	0	4	0
48 h	0	4[d a]	2	0	4	1
72 h	0	4[d a]	4[a]	0	4	2
mean (24-72 h)	**0.0**	**3.3**	**2.3**	**0.0**	**4.0**	**1.0**
6 d	-	4[e a]	4[a]	-	3	1
8 d	-	4[e a]	4[a]	-	2	0
10 d	-	1[c]	4[b]	-	1	0
14 d	-	0	0[c]	-	0	0

- not examined.
[a] eschar formation.
[b] eschar partly desquamated.
[c] eschar completely desquamated, normal skin beneath desquamated eschar.
[d] alteration, focal, black, 3 mm diameter.
[e] alteration, focal, red, 3 mm diameter.

Table A.43(b) Results of the acute dermal irritation/corrosion study in rabbits (**Doc IIIA A6.1.4/02**)

Animal number		1	2	3	4	5	6
Erythema & Eschar	4.5 – 5 hr	1	0	1	2	1	0

formation	24 hr	1	1	0	1	1	2
	48 hr	1	1	0	0	1	2
	72 hr	0	0	0	0	0	1
Mean score (24, 48, 72 hrs)		0.7	0.7	0	0.3	0.7	1.7
Edema	4.5 – 5 hr	0	1	1	2	2	0
	24 hr	0	0	0	0	1	1
	48 hr	0	0	0	0	0	1
	72 hr	0	0	0	0	0	0
Mean score (24, 48, 72 hrs)		0	0	0	0	0.3	0.7

Table A.43(c) Results of the acute dermal irritation/corrosion study in rabbits (BPR Art. 95 dossier, 2014)

Animal	1			2			3		
Time after exposure	Erythema (0-4)	Oedema (0-4)	comments	Erythema (0-4)	Oedema (0-4)	comments	Erythema (0-4)	Oedema (0-4)	comments
1 hour	0	0	-	0	0	-	0	1	-
24 hours	0	0	-	1	0	-	1	1	-
48 hours	0	0	-	0	0	-	0	0	-
72 hours	0	0	-	0	0	-	0	0	-
Mean score (24, 48 and 72 hours)	0	0		0.3	0		0.3	0.3	

Table A.43(d) Results of the acute dermal irritation/corrosion study in rabbits: Individual daily and mean scores for dermal irritation following 4 hour exposure (REACH registration dossier, JS member, Opt-out, 2014)

Skin reaction	Reading (hours)	Individual scores – Rabbit Number and sex (bodyweight in Kg)		
		5 female (2.38)	6 female (2.72)	16 female (2.78)
Erythema/eschar formation	24	2	2	2
	48	1	1	1
	72	0	0	0
Total		3	3	3
Mean score		1	1	1
Oedema formation	24	1	1	1
	48	0	0	0
	72	0	0	0
Total		1	1	1
Mean score		0.3	0.3	0.3

Table A.43 Summary table of human data on skin corrosion/irritation
No human data is available.

A3.3.1 Short summary and overall relevance of the provided information on skin corrosion/irritation
The acute skin irritation potential of sodium pyrithione was investigated in four acute dermal irritation/corrosion studies. In the first study (Doc IIIA A6.1.4/01) severe erythema were noted in 2 out of 3 animals. Eschar was formed subsequently but finally desquamated and skin was normal again at the end of the observation period. In all animals oedema were noted already after the patch removal. Whereas 1/3 animals was free from oedema from 24 h p.a. onwards, oedema in different grades of severity were noted in the other two animals until 6 or 10 days p.a. Skin lesions at the application sites were reversible within 14 days p.a. The mean score from gradings at 24, 48 and 72 hours in the three animals for erythema/eschar was 0, 3.3 and 2.3 and that for oedema was 0, 4 and 1.

In the second study (Doc IIIA A6.1.4/02) slight erythema was noted at 4.5 - 5, 24, 48, and 72 hours and oedema was absent to slight at 4.5 - 5, 21, 48, and 72 hours. The mean score from gradings at 24, 48 and 72 hours for erythema/eschar or oedema for all animals was < 2.3. In the third study (BPR Art. 95 dossier, 2014) slight erythema was noted in 2 animals at 24 hours and slight oedema was noted in 1 animal at 1 and 24 hours. The mean score from gradings at 24, 48 and 72 hours for erythema or oedema

for all animals was < 2.3. In the fourth study (REACH registration dossier, JS member, Opt-out, 2000) "Well define erythema and slight oedema were noted in all treated skin sites at the 1 hour observation period with well define erythema and very slight oedema at the 24 hour observation. Very slight erythema was noted at all treatment sites at the 48 hour observation. All treated skin sites appeared normal at the 72 hour observation period. The findings for the three animals at each timepoint were the same". The mean score from gradings at 24, 48 and 72 hours for erythema or oedema for all animals was < 2.3.

Sodium pyrithione was also tested in an *in vitro* skin irritation test (reconstructed human epidermis test method; EPISKIN Small Model™) (BPR Art. 95 dossier, 2014). 25 µl of sodium pyrithione was applied for 15 minutes on top the skin tissue. After 42 hour post-treatment incubation period the cytotoxic effect (irritancy) was performed. The relative mean tissue viability for sodium pyrithione compared to negative controls was 114%. Since the tissue viability was > 50%, sodium pyrithione is considered to be non-irritant under the test conditions.

A 3.3.2 Comparison with the CLP criteria
Skin corrosion is defined as the production of irreversible damage to the skin and skin irritation is defined as the production of reversible damage to the skin following the application of a test substance for up to 4 hours (Annex I: 3.2.1.1). Classification of a substance for skin irritation (Category 2) is required on the basis of an animal study showing a mean score (24-72 hour) of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested or, if reactions are delayed, from three consecutive days after the onset of skin reactions. Classification is also required for inflammation that persists to the end of the observation period (normally 14 days) in at least 2 animals, particularly taking into account findings such as alopecia, hyperkeratosis, hyperplasia, and scaling. Classification may also be required in some cases where there is pronounced variability of response among animals, with very definite positive effects related to exposure in a single animal but less than the criteria listed above.

Since sodium pyrithione showed a mean score (24-72 hour) of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema in 2 of 3 New Zealand white rabbits in an OECD 404 compliant study performed in accordance with the GLP (Doc IIIA A6.1.4/01), it should be classified for skin irritation (Category 2).

A3.3.3 Conclusion on classification and labelling for skin corrosion/irritation
Based on the available data, the DS proposes classification for skin irritation (Category 2) for sodium pyrithione according to the CLP criteria. The corresponding hazard statement is H315: Causes skin irritation.

A3.3.4 Overall conclusion on skin irritation and corrosivity related to risk assessment
Not applicable for the CLH report.

A.3.4. Serious eye damage and Eye irritation

Table A.44 Summary table of in vitro studies on serious eye damage and eye irritation

Summary table of in vitro studies on serious eye damage and eye irritation

<table>
<tr><th>Method, Guideline, GLP status, Reliability, Key/supportive study</th><th>Test substance (including purity), Vehicle, Doses</th><th>Relevant information about the study</th><th>Results</th><th>Remarks (e.g. major deviations)</th><th>Reference</th></tr>
<tr><td>Bovine Corneal Opacity and Permeability test, OECD 437, GLP: yes, Supporting study</td><td>Sodium pyrithione (40.8% aqueous solution), Vehicle: none, Amount of test substance applied: 750 µl</td><td>Negative control: physiological saline

Positive control: 10% (w/v) benzalkonium chloride solution prepared in physiological saline

Each group (test substance, negative, and positive controls) consisted of 3 eyes

Treatment period: 10 minutes</td><td>Sodium pyrithione did not induce ocular irritation through both endpoints (opacity and permeability), resulting in a mean in vitro irritancy score (IVIS) of 0.8.

<table>
<tr><th>Treatment</th><th>Mean Opacity [1]</th><th>Mean Permeability [1]</th><th>Mean In vitro Irritation Score [1, 2]</th></tr>
<tr><td>Negative control</td><td>0</td><td>0.000</td><td>0.0</td></tr>
<tr><td>Positive control (Benzalkonium Chloride)</td><td>75</td><td>3.174</td><td>122.6</td></tr>
<tr><td>Sodium pyrithione</td><td>1</td><td>-0.012</td><td>0.8</td></tr>
</table>
1 Calculated using the negative control mean opacity and mean permeability values.
2 In vitro irritancy score (IVIS) = mean opacity value + (15 x mean OD_{490} value).</td><td>-</td><td>BPR Art. 95 dossier

Year: 2014(c)

(unpublished)</td></tr>
</table>

Table A.45 Summary table of animal studies on serious eye damage and eye irritation

Summary table of animal studies on serious eye damage and eye irritation					
Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/group	Test substance (including purity), Vehicle, Dose levels Duration of exposure	Results Average score for corneal opacity, iritis, conjunctival redness and conjunctival oedema (24, 48, 72 h) per animal, observations and time point of onset, reversibility	Remarks (e.g. major deviations)	Reference
Acute eye irritation/corros	Rabbit, New	Sodium pyrithione (40% aqueous	There was no corneal opacity noted at any observation period.	-	Doc IIIA A6.1.4/03

<table>
<tr>
<td>ion test,
14 days
OECD 405,
GLP: yes,
Reliability: 1,
Key study</td>
<td>Zealand White,
6 females</td>
<td>solution),
Vehicle: none,
Amount of test substance instilled: 0.1 ml,
Exposure period: 24 hours,
Examination time points: 60 min, 1, 2, 3, 7 and 14 days.</td>
<td>Iritis, noted in 6/6 eyes, cleared by Day 2.
Conjunctival irritation, noted in 6/6 eyes, cleared by Day 14.
Three animals died by Day 2 with predeath signs of lethargy, prostration, soiling of the anogenital area, convulsions, tachypnea, ataxia, and wetness of the nose/mouth area. Physical signs noted in survivors included lethargy, yellow nasal discharge, and yellow staining of the nose/mouth area.
Necropsy of the animals that died during the study revealed abnormalities of the lungs, peritoneal cavity, and gastrointestinal tract, as well as wetness of the nose/mouth area and yellow nasal discharge.
<table>
<tr><th rowspan="2">Animal</th><th colspan="4">Mean scores at day 1, 2, and 3</th></tr>
<tr><th>Cornea</th><th>Iris</th><th>Conjunctival redness</th><th>Conjunctival oedema</th></tr>
<tr><td>1</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>2</td><td>0</td><td>0</td><td>2</td><td>0</td></tr>
<tr><td>3</td><td>0</td><td>0</td><td>3</td><td>0.3</td></tr>
<tr><td>4</td><td>0</td><td>1</td><td>2</td><td>1</td></tr>
<tr><td>5</td><td>0</td><td>0</td><td>1.7</td><td>0.3</td></tr>
<tr><td>6</td><td>0</td><td>0</td><td>2</td><td>0.7</td></tr>
</table>
</td>
<td></td>
<td>Year: 1996

(unpublished)</td>
</tr>
<tr>
<td>Acute eye irritation/corrosion test,
72 hours
OECD 405,
GLP: yes,
Reliability: 1,
Key study</td>
<td>Rabbit, New Zealand White,
6 females</td>
<td>Sodium pyrithione (40% aqueous solution),
Vehicle: none,
Amount of test substance instilled: 0.01 ml,
Exposure period: 24 hours,
Examination time points: 60 min, 1, 2 and 3 days.</td>
<td>Two animals died by Day 2 with predeath signs of convulsions, prostration, shallow breathing, wetness of the nose/mouth area, and abnormal posture.
Three of the four surviving animals appeared normal during the observation period. Wetness of the nose/mouth area and yellow nasal discharge were noted in survivors.
Corneal opacity was noted in one eye on Day 1, but cleared by Day 2. Iritis was noted in two eyes on Day 1. Conjunctival irritation was noted in six eyes, but cleared by Day 3 in the surviving animals.
<table>
<tr><th rowspan="2">Animal</th><th colspan="4">Mean scores at day 1, 2, and 3</th></tr>
<tr><th>Cornea</th><th>Iris</th><th>Conjunctival redness</th><th>Conjunctival oedema</th></tr>
<tr><td>1</td><td>0</td><td>1</td><td>2</td><td>1</td></tr>
</table>
</td>
<td>-</td>
<td>Doc IIIA A6.1.4/04

Year: 1996

(unpublished)</td>
</tr>
</table>

			2	0.3	0	0	0
			3	0	0	0	0
			4	0	1	1	0
			5	0	0	0	0
			6	0	0	0.3	0
Acute eye irritation/corrosion test, 7 days, OECD 405, GLP: yes, Reliability: 1, Key study	Monkey, Cynomolgous, 2 males and 1 female	Sodium pyrithione (40% aqueous solution), Vehicle: none, Amount of test substance instilled: 0.1 ml, Exposure period: 24 hours, Examination time points: 60 min, 1, 2, 3, 4 and 7 days	There were no deaths, clinical findings or remarkable changes in body weights during the study period. The maximum average score was 2.0 at 48 hours post-instillation. A positive conjunctival reaction was noted in the treated eye of one male animal. Minor conjunctival irritation was observed for the other male while no ocular irritation was noted for the female. There were no corneal or irridial findings. All irritation was reversible and completely subsided by Day 7. No signs of systemic toxicity were observed.				-	Doc IIIA A6.1.4/02 Year: 1997 (unpublished)

Animal	Mean scores at day 1, 2, and 3			
	Cornea	Iris	Conjunctival redness	Conjunctival oedema
1 (male)	0	0	1	0
2 (male)	0	0	1.3	0
3 (female)	0	0	0	0

<table>
<tr>
<td>Acute eye irritation/corrosion test,
7 days,
OECD 405,
GLP: yes,
Reliability: 1,
Key study</td>
<td>Rabbit, New Zealand White,
3 males</td>
<td>Sodium pyrithione (40.8% aqueous solution),
Vehicle: none,
Amount of test substance instilled: 0.1 ml,
Exposure period: eye not rinsed after instillation,
Examination time points: 60 min, 1, 2, 3 and 7 days</td>
<td>Three animals showed irritation of the conjunctivae, which consisted of redness, chemosis and discharge. The irritation had completely reversed within 7 days.

No irridial irritation or corneal opacity was observed in any of the animal.

There was no evidence of ocular corrosion.

There was no mortality or systemic toxicity.

<table>
<tr><th rowspan="2">Animal</th><th colspan="4">Mean scores at day 1, 2, and 3</th></tr>
<tr><th>Cornea</th><th>Iris</th><th>Conjunctival redness</th><th>Conjunctival oedema</th></tr>
<tr><td>1</td><td>0</td><td>0</td><td>1.7</td><td>1</td></tr>
<tr><td>2</td><td>0</td><td>0</td><td>1.7</td><td>0.7</td></tr>
<tr><td>3</td><td>0</td><td>0</td><td>1.7</td><td>0.3</td></tr>
</table>
</td>
<td>-</td>
<td>BPR Art. 95 dossier

Year: 2014(a)

(unpublished)</td>
</tr>
</table>

Acute eye irritation/corrosion test, 24 hours, OECD 405, GLP: yes, Reliability: 1, Key study	Rabbit, New Zealand White, 1 male and 1 female, 2/group	Sodium pyrithione (purity: >95%), Vehicle: none, Amount of test substance instilled: 78.1 mg (74.6 – 81.5 mg), Exposure period: : eye not rinsed after instillation, Examination time points: 1 (both animals) and 24 hours (one animal)	One animal was found dead on Day 2. The other animal was sacrificed on Day 2 for humane reasons when it was seen undergoing severe spasms for approx. 15 minutes followed by total lethargy and severe spasms. Macroscopic findings in the animal found dead included swelling and dark red discolouration of the conjunctivae of the treated eye and the many dark red foci in the thymus. Macroscopic findings in the animal sacrificed included swelling of the upper and lower eyelids, and dark red discolouration of the conjunctivae of the treated eye. Both animals at 1 hour and the sacrificed animal at 24 hours showed irritation of the conjunctivae in the form of redness (maximum grade 2), chemosis (maximum grade 2) and discharge (maximum grade 2). No irridial irritation or corneal opacity was observed in either animal. There was no evidence of ocular corrosion.	Sodium pyrithione caused mortality after instillation into the rabbit eye at approx. 23 mg/kg.	BPR Art. 95 dossier Year: 2014(b) (unpublished)

<table>
<tr>
<td>Acute eye irritation/corrosion test,
72 hours,
OECD 405,
GLP: yes,
Reliability: 1,
Key study</td>
<td>Rabbit,
New Zealand White,
3 females</td>
<td>Sodium pyrithione (41.1% aqueous solution),
Vehicle: none,
Amount of test substance instilled: 0.1 ml,
Exposure period: eye not rinsed after instillation,
Examination time points: 60 min, 1, 2, 3 and 7 days</td>
<td>"No corneal or irridial effects were noted during the study. Minimal conjunctival irritation was noted in all treated eyes for one hour after treatment and in two treated eyes at the 24 hour observation. One treated eye appeared normal at the 24 hour observation and the remaining two treated eyes appeared normal at the 48 hour observation."

"No clinical signs or evidence of systemic toxicity was noted."
<table>
<tr><th rowspan="2">Animal</th><th colspan="4">Mean scores at day 1, 2, and 3</th></tr>
<tr><th>Cornea</th><th>Iris</th><th>Conjunctival redness</th><th>Conjunctival oedema</th></tr>
<tr><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>2</td><td>0</td><td>0</td><td>0.3</td><td>0</td></tr>
<tr><td>3</td><td>0</td><td>0</td><td>0.3</td><td>0</td></tr>
</table>
</td>
<td>The DS doesn't have access to the full study report.</td>
<td>REACH registration dossier,
JS member,
Opt-out

Year: 2005</td>
</tr>
</table>

Table A.46 Summary table of human data on serious eye damage and eye irritation
No human data is available.

A3.4.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation
The acute eye irritation/corrosion potential of sodium pyrithione was investigated in six *in vivo* studies (five with rabbits and one on monkeys) and in an *in vitro* test.

In the first rabbit study (Doc IIIA A6.1.4/03), there was no corneal opacity noted at any observation period. Iritis, noted in 6/6 eyes, cleared by day 2. Conjunctival irritation, noted in 6/6 eyes, cleared by day 14. Three animals died by day 2 with predeath signs of lethargy, prostration, soiling of the anogenital area, convulsions, tachypnea, ataxia, and wetness of the nose/mouth area. Physical signs noted in survivors included lethargy, yellow nasal discharge, and yellow staining of the nose/mouth area.

In the second rabbit study (Doc IIIA A6.1.4/04), two animals died by day 2 with predeath signs of convulsions, prostration, shallow breathing, wetness of the nose/mouth area, and abnormal posture. Three of the four surviving animals appeared normal during the observation period. Wetness of the nose/mouth area and yellow nasal discharge were noted in survivors. Corneal opacity was noted in one eye on day 1, but cleared by day 2. Iritis was noted in two eyes on day 1. Conjunctival irritation was noted in six eyes, but cleared by day 3 in the surviving animals. The test article produced corneal opacity and irritation which cleared by day 3. However, the clinical signs and toxicity produced by this application indicates that the material is toxic to rabbits via this route. Necropsy of the

animals that died during the study revealed abnormalities of the lungs, peritoneal cavity, and gastrointestinal tract, as well as wetness of the nose/mouth area and yellow nasal discharge. The test article produced irritation which cleared within 14 days.

In the monkey study (Doc IIIA A6.1.4/02), there were no deaths or clinical findings during the study period. The maximum average score was 2.0 at 48 hours post-instillation. A positive conjunctival reaction was noted in the treated eye of one male animal. Minor conjunctival irritation was observed for the other male while no ocular irritation was noted for the female. There were no corneal or irridial findings. All irritation was reversible and completely subsided by day 7. No signs of systemic toxicity were observed.

In the third rabbit study (BPR Art. 95 dossier, 2014(a)), three animals showed irritation of the conjunctivae, which consisted of redness, chemosis and discharge. The irritation had completely reversed within 7 days. No irridial irritation, corneal opacity or evidence of ocular corrosion was observed in any of the animal. There was no mortality or systemic toxicity.

In the fourth rabbit study (BPR Art. 95 dossier, 2014(b)), one animal was found dead on Day 2. The other animal was sacrificed on Day 2 for humane reasons when it was seen undergoing severe spasms for approx. 15 minutes followed by total lethargy and severe spasms. Macroscopic findings in the animal found dead included swelling and dark red discolouration of the conjunctivae of the treated eye and the many dark red foci in the thymus. Macroscopic findings in the animal sacrificed included swelling of the upper and lower eyelids, and dark red discolouration of the conjunctivae of the treated eye. Both animals at 1 hour and the sacrificed animal at 24 hours showed irritation of the conjunctivae in the form of redness (maximum grade 2), chemosis (maximum grade 2) and discharge (maximum grade 2). No irridial irritation, corneal opacity or evidence of ocular corrosion was observed in either animal. In this study sodium pyrithione caused mortality after instillation into the rabbit eye at approx. 23 mg/kg.

In the fifth rabbit study (REACH registration dossier, JS member, Opt-out, 2005), "No corneal or iridial effects were noted during the study. Minimal conjunctival irritation was noted in all treated eyes for one hour after treatment and in two treated eyes at the 24 hour observation. One treated eye appeared normal at the 24 hour observation and the remaining two treated eyes appeared normal at the 48 hour observation." "No clinical signs or evidence of systemic toxicity was noted." The DS doesn't have access to the full study report.

In a Bovine Corneal Opacity and Permeability test (BPR Art. 95 dossier, 2014(c)), sodium pyrithione did not induce ocular irritation through both endpoints (opacity and permeability), resulting in a mean *in vitro* irritancy score (IVIS) of 0.8 after 10 minutes of treatment. Therefore, under the test conditions, sodium pyrithione was found to not induce serious eye damage or eye irritation.

A3.4.2 Comparison with the CLP criteria

Serious eye damage (Category 1) is defined as the production of tissue damage in the eye, or serious physical decay of vision, following application of a substance to the anterior surface of the eye, which is not fully reversible within 21 days of application (Annex I: 3.3.1.1).

Eye irritation (Category 2) is defined as the production of changes in the eye following the application of test substance to the anterior

surface of the eye, which are fully reversible within 21 days of application (Annex I: 3.3.1.1).

Classification in Category 1 is required for substances producing in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days. Classification is also required for substances producing in at least 2 of 3 animals a positive response of mean (24-72 hour) scores of ≥ 3 for corneal opacity and/or > 1.5 for iritis.

Classification in Category 2 is required for substances producing in at least 2 of 3 animals a positive response of mean (24-72 hour) scores of ≥ 1 for corneal opacity and/or ≥ 1 for iritis and/or ≥ 2 for conjunctival redness and/or ≥ 2 for conjunctival oedema which fully reverses within an observation period of normally 21 days.

In the first study conjunctival redness was noted in 4 animals with mean (24-72 hour) scores ≥ 2. Therefore, sodium pyrithione should be classified for eye irritation (category 2).

Application of sodium pyrithione to eyes of the rabbits resulted in mortality in three different studies (Doc IIIA A6.1.4/03, Doc IIIA A6.1.4/04 and BPR Art. 95 dossier, 2014(b)). Therefore, a supplemental labelling phrase EUH070 'Toxic by eye contact' is required for sodium pyrithione.

A3.4.3 Conclusion on classification and labelling for serious eye damage/eye irritation
Based on the available data, the DS proposes classification for eye irritation (Category 2) for sodium pyrithione according to the CLP criteria. The corresponding hazard statement is H319: Causes serious eye irritation.

Furthermore, a supplemental labelling phrase EUH070 'Toxic by eye contact' is required for sodium pyrithione.

A3.4.4 Overall conclusion on eye irritation and corrosivity related to risk assessment
Not applicable for the CLH report.

A.3.5. Skin sensitisation

Table A.47 Summary table of animal studies on skin sensitisation

Summary table of animal studies on skin sensitisation					
Method, Duration of study, Route of exposure (e.g. topical/intradermal, induction/challenge if relevant),	Species, Strain, Sex, No/group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results (e.g. EC3-value or amount of sensitised animals at induction dose)	Remarks (e.g. major deviations)	Reference

Guideline, GLP status, Reliability, Key/supportive study					
Guinea Pig Maximisation Test (Magnusson-Kligman), Induction: intradermal and topical; Challenge: topical application, OECD 406, GLP: yes, Reliability: 1, Key study	Guinea pigs, Dunkin Hartley, Female, 2 x 10 (2 additional animals) for the test substance group 2 x 5 for the control group	Sodium pyrithione (purity: < 95%), Water, 5 % for intradermal induction exposure and 50 % for topical induction (48 hr) and challenge exposure (24 hr)	24 and 48 hours after the end of challenge exposure 2/16 animals were sensitised. ↑ mortality (4 animals after topical induction) Fore limb paralysis in one animal ↓ well-being ↓ body weight	The test substance is toxic by the epicutaneous exposure	Doc IIIA A6.1.5/01 Year: 2002 (unpublished)
Guinea Pig Maximisation Test (Magnusson-Kligman), Induction: intradermal and topical; Challenge: topical application, OECD 406, GLP: yes, Reliability: 1, Key study	Guinea pigs, Hartley Albino, Male, 10 animals for test substance group	Sodium pyrithione (43.7% aqueous solution; purity not specified), Water, 10 % for intradermal and topical induction exposure (48 hr) and 5% for challenge exposure (24 hr)	24.5 and 48 hours after the end of challenge exposure 2/10 and 3/10 animals were sensitised, respectively.	No controls were used. There is no information on toxicity in the report.	Doc IIIA A6.1.5/02 Year: 1987 (unpublished)
Local lymph node assay, Topical application, OECD 429, GLP: yes, Reliability: 1,	Mice, CBA/J, Female, 5 animals per test substance and control	Sodium pyrithione (purity: > 95%), Vehicle: 1% watery Pluronic L92, Dose levels: 5, 10, 15 and 25%	The SI values at 5, 10, 15, and 25% were 1, 1.8, 2.5, and 7.2, respectively. In the 25% group one animal had irritation of the ears and reduced body weight (- 2 grams). All animals in the	The dose levels initially selected were 5, 10 and 25%. An	BPR Art. 95 dossier Year: 2014 (unpublish

Key study	groups	Induction on Days 1, 2 and 3 Necropsy on Day 6	group had enlarged ears on Days 5 and 6. Two animals had ear thickness above 25% and these were therefore excluded from interpretation. In the 15% group one animal had piloerection and ptosis on Day 2 and another animal had reduced body weight (- 2 grams). There were no toxicological effects in the 10 and 5% groups.	additional vehicle group and a 15% level was included later to further characterise dose-response.	ed)
Similar to local lymph node assay, Topical application, Similar to OECD 429, GLP: yes, Reliability: 1,	Mice, Balb/c, Male, 4 animals	Sodium pyrithione, Vehicle: Dimethylformamide Dose levels: 0.25, 2.5 and 25% Induction on Days 0, 1 and 2 Necropsy on Day 5	The SI values at 0.25 and 2.5%, were 1.6 and 4.58, respectively. "Due to a technical error during preparation of the single cell suspension, the results of the highest concentration (25% w/v) were not representative, and have therefore been discarded."	The DS doesn't have access to the full study report.	REACH registration dossier, JS member, Opt-out Year: 2000

Table A.48(a)(i) First GPMT: Induction/challenge/scoring schedule (**Doc IIIA A6.1.5/01**)

	GPMT		**Observations/Remarks**	
	day	application	negative control group	test substance group
Induction 1	0	intradermal	severe irritations	severe irritations

Pre-treatment for non-irritating substances	6	n-dodecylsulfate, sodium salt, in white petrolatum	-	-
Induction 2	7-9	topical	severe irritations	severe irritations
Challenge	21-22	topical	1/10 animals with slight erythema	2/16 animals with severe irritations
(rechallenge)	not applied	n.a.	n.a.	n.a.

Table A.48(a)(ii) First GPMT: results (**Doc IIIA A6.1.5/01**)

	Number of animals with signs of allergic reactions / number of animals in group		
	Negative control	Test group	Positive control
scored after 24h	1/ 10	2 / 16	7 / 10
scored after 48h	1 / 10	2 / 16	7 / 10

Table A.48(b) Second GPMT: results (**Doc IIIA A6.1.5/02**)

	INDUCTION A												INDUCTION B	CHALLENGE	
SITE:	A Left		A Right		B Left		B Right		C Left		C Right		2 x 4 cm	5 x 5 cm	
HOUR:	24	48	24	48	24	48	24	48	24	48	24	48	48	24½	48
	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
AN. # & SEX															
A6451	2^{b}	2	2^{b}	1	2^{bg}	2^{b}	2^{bg}	2^{b}	2^{gb}	2^{gb}	2^{b}	2^{b}	2_{p}	0	0
A6452	2	2_{b}	2	1_{f}	2^{bg}	4	2^{gb}	4	2_{b}	2_{b}	2_{b}	2^{b}	2^{p}	1	0
A6453	2	2^{bf}	2	2^{f}	2^{b}	4	2^{gb}	4	2^{b}	2^{b}	2^{b}	1^{b}	3^{p}	0	0
A6454	2	1^{b}	2	1	2^{bg}	4	2^{gb}	4	2^{b}	4_{fp}	2^{b}	4_{fp}	1	0	0
A6455	2	1^{b}	2	1_{f}	2^{bg}	4	2^{bg}	4	2	2^{fp}	2	2^{fp}	2	0	0
A6456	2	1_{f}	2	2_{f}	2^{b}	4_{g}	2^{b}	4_{g}	3_{gb}	4_{g}	4_{gb}	2_{g}	3	0	0
A6457	2	2^{f}	2	3^{f}	2^{gb}	4^{g}	2^{gb}	4^{g}	2^{gb}	4^{f}	2^{gb}	4^{fb}	2	0	1
A6458	2	2	2	1^{f}	2^{b}	4	2^{gb}	2^{gb}	2	2^{bp}	2	2^{bp}	2^{p}	1	1
A6459	2	2_{f}	2	2_{f}	2^{b}	4_{b}	2^{b}	4	2^{p}	2^{bp}	2^{bp}	2^{bp}	2^{p}	0	0
A6460	2	1^{f}	2	1^{f}	2^{b}	2^{b}	2^{b}	4	2^{p}	1^{bp}	2^{bp}	1^{bp}	3	0	1

CODE: R = erythema (redness)
b = brown areas
e = eschar
f = skin flaking
g = green areas
p = pale areas

Evaluation of skin reaction: No reaction: 0; Scattered mild redness: 1; Moderate or diffuse redness: 2; Intense redness & swelling: 3.

Table A.48(c) LLNA in CBA/J: relative size lymph nodes, radioactivity counts (DPM) and stimulation index (SI) (**BPR Art. 95 dossier, 2014**)

group	TS [1] (%)	animal	Size nodes [2] left	Size nodes [2] right	DPM [3] / animal	mean DPM ± SEM [4]	mean SI ± SEM
1	0	1	n	n	369		
		2	n	n	349		
		3	n	n	324	425 ± 52	1.0 ± 0.2
		4	n	n	605		
		5	n	n	476		
2	5	6	n	n	340		
		7	n	n	554		
		8	n	n	426	409 ± 40	1.0 ± 0.2
		9	n	n	338		
		10	n	n	387		
3	10	11	n	n	820		
		12	n	n	781		
		13	n	n	750	763 ± 17	1.8 ± 0.2
		14	n	n	719		
		15	n	n	743		
4	25	16	+	+	3323		
		17	+	+	3058		
		18	+	+	2729	3037 [5] ± 172	7.2 [5] ± 1.0
		19 [5]	+	+	2552 [5]		
		20 [5]	+	+	4232 [5]		
5	0	21	n	n	337		
		22	n	n	324		
		23	n	n	103	251 ± 45	1.0 ± 0.3
		24	n	n	192		
		25	n	n	300		
6	15	26	n	n	1138		
		27	n	n	724		
		28	n	n	213	636 ± 173	2.5 ± 0.8
		29	n	n	282		
		30	n	n	823		

1. TS = test substance (% w/w).
2. Relative size auricular lymph nodes (-, -- or ---: degree of reduction, +,++ or +++: degree of enlargement, n: considered to be normal).
3. DPM = Disintegrations per minute
4. SEM = Standard Error of the Mean
5. Animal nos. 19 and 20 had ear thickness measurements that exceeded 25%. These animals were excluded from calculation as the increase in ear thickness was above criterion and may have had a toxicologically relevant effect on the activity of the nodes. When recalculated excluding their values the mean DPM/animal value for the 25% concentration was 3179 DPM and the SI value was 7.5.

Table A.48 Summary table of human data on skin sensitisation

Summary table of human data on skin sensitisation				
Type of data/report, Reliability**, Key/supportive study	Test substance (including purity), Vehicle	Relevant information about the study (e.g. description of the test subjects (general population/selected/unselected dermatitis patients/workers), exposure data (induction dose, daily and overall exposure)	Main effects, Observations	Reference
Diagnostic patch test, Reliability: reliable – published article; method described, Supportive study	Sodium pyrithione (20% aqueous solution), Water Concentration: 1%	230 workers from the metallurgical industry and with occupational dermatitis were studied with patch tests (scored at 48 and 96 hours).	Negative	Alomar et al., 1985[6]
Diagnostic patch test, Reliability: reliable – published article; method described, Supportive study	Sodium pyrithione (40% aqueous solution), Water, Concentration: 1%	40 workers exposed to metalworking fluids and with acute dermatitis were studied with patch tests (48 hours occlusive contact followed by scoring at 72 hours).	Negative. One out of 24 control persons was positive which was considered possibly due to excessive use of antidandruff shampoos.	DeBoer et al., 1988[7]
Diagnostic patch test, Reliability: reliable – published article; method described, Supportive study	Sodium pyrithione (40% aqueous solution), Water, Concentration: 0.1%	115 workers exposed to cutting oils and with dermatitis were studied with patch tests (48 hours occlusive contact followed by scoring at 48 and 96 hours).	Negative	English and Rycroft, 1989[8]
Diagnostic patch test, Reliability: reliable –	Sodium pyrithione (40% aqueous	A 45 year old female worker frequently exposed to metal working	Positive.	Tosti et al.,

[6] Alomar, A., Conde-Salazar, C. and Romaguera, C. 1985. Occupational dermatoses from cutting oils. Contact Dermatitis 12: 129–138.
[7] De Boer, E.M., Van Ketel, W.G. and Bruynzeel, D.P. 1989. Dermatoses in metal workers (II). Allergic contact dermatitis. Contact Dermatitis 20: 280–286.
[8] English, J.S.C. and Rycroft, J.R.G. 1989. Cutting Oil Dermatitis: A Review of 115 Patients. Frosch PJ, Gooms-Doossens A, Lachapelle JM, Rycroft RJG, Scheper RJ (Eds): Current topics in contact dermatitis, Springer, Berlin, Heidelberg, 212–215.

published article; method described, Supportive study	solution), Water, Concentration: 0.3%	fluids for 10 years had subacute eczema of the backs of her hands and fingers dating from 1 month previously. After standard patch tests including the cutting-oils, she was patch tested with sodium pyrithione (scored at 48, 72 and 96 hours).	Patch tests with the same concentration of sodium pyrithione in 10 adult volunteers were negative.	1990[9]

Table A.49 Summary table of other studies relevant for skin sensitisation
No other relevant studies are available.

A3.5.1 Short summary and overall relevance of the provided information on skin sensitisation
The sensitising potential of sodium pyrithione was investigated in two GPMTs and two LLNAs. In the first GPMT study (Doc IIIA A6.1.5/01), sodium pyrithione concentration for induction was 5% intradermal injection, and 50% epicutaneous application. Six animals treated with sodium pyrithione died after the end of the epicutaneous induction exposure. Their deaths were considered test related but the cause of death remains unknown. In one animal fore limb paralysis was noted and reduced well-being were observed in all test substance treated animals after end of epicutaneous challenge exposure and mean body weights of the test substance group animals were lower than those of controls. 50% sodium pyrithione was used for epicutaneous challenge exposure for a duration of 24 h. After the challenge exposure, 2/16 (i.e. 12.5%) animals of the test substance group had positive skin reactions 24 h and 48 h after the end of the exposures.

In the second GPMT study (Doc IIIA A6.1.5/02) ten male guinea pigs received 2 induction doses and 1 challenge dose of sodium pyrithione. The first induction dose was administered intradermally at a concentration of 10% of test material together with Freund's adjuvant. The second dose was a topical dose of the test material only, also at a concentration of 10%, occluded for 48 hours. If sodium pyrithione was not irritating, the skin was irritated by applying 10% sodium lauryl sulphate before patch application. The challenge was a topical dose of the test material, occluded for 24 hours and administered 21 days after the first dose. Following a 24 hour exposure to a 5% dilution of challenging sodium pyrithione, mild erythema was observed in 2/10 (20%) animals 24.5 hours post dose. At 48 hours, 3/10 (30%) animals had mild erythema.

In an LLNA in CBA/J mice (BPR Art. 95 dossier, 2014) performed according to the guideline OECD 429 and in accordance with the GLP, sodium pyrithione was tested in 5 females per group at the concentrations of 0, 5, 10, 15 and 25%. The SI values at those levels were 1, 1.8, 2.5 and 7.2 respectively. Therefore, by interpolation, the EC3 value is calculated as 16%.

In another LLNA in Balb/c mice (REACH registration dossier, JS member, Opt-out, 2000) performed according to guidelines similar

[9] Tosti, A., Piraccini, B. and Brasile, G.P. 1990. Occupational contact dermatitis due to sodium pyrithione. Short communication - Contact Dermatitis 1990; 22: 118.

to OECD 429 and in accordance with the GLP, sodium pyrithione was tested in 4 males per group at the concentrations of 0.25, 2.5 and 25%. It was reported in the study summary that "Due to a technical error during preparation of the single cells suspension, the results of the highest concentration (25% w/v) were not representative, and have therefore been discarded." The DS does not have access to the full study report. The SI values at 0.25 and 2.5% were 1.6 and 4.58, respectively. Therefore, by interpolation, the EC3 value is calculated as 1.3%. The DS doesn't have access to the full study report.

Four reports of diagnostic patch test data with sodium pyrithione are also available. Sodium pyrithione at 1% or 0.1% concentration was found to be negative in 230 (Alomar et al., 1985), 40 (DeBoer et al., 1988) and 115 (English and Rycroft, 1989) metallurgical industry workers with occupational dermatitis. Sodium pyrithione at 0.3% concentration was found to be positive after patch testing of a 45 year old female working for 10 years in the metallurgical industry. However, patch tests with the same concentration of sodium pyrithione in 10 adult volunteers were negative (Tosti et al., 1990).

A3.5.2 Comparison with the CLP criteria

Substances are classified as Category 1 skin sensitisers where data are not sufficient for sub-categorisation, if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or if there are positive results from an appropriate animal test.

Substances are classified as Category 1A skin sensitisers where there is evidence of a high frequency of occurrence in humans and/or a high potency in animals. Such evidence includes

> Human evidence: diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure
>
> GPMT: ≥30% responding at ≤0.1% intradermal induction dose or ≥60% responding at >0.1% to ≤1% intradermal induction dose.
>
> LLNA: EC3 value ≤2%.

Substances are classified as Category 1B skin sensitisers where there is evidence of a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals. Such evidence includes

> Human evidence: diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure
>
> GPMT: ≥30% to <60% responding at >0.1% to ≤1% intradermal induction dose or ≥30% responding at >1% intradermal induction dose.
>
> LLNA: EC3 value >2%.

The available human data on sodium pyrithione indicates relatively low frequency of skin sensitisation at relatively low exposure suggesting Category 1. In one of the two GPMTs, 30% of the animals were positive at >1% intradermal induction dose of sodium pyrithione suggesting Category 1B. In one LLNA sodium pyrithione showed an EC3 value of 16% suggesting Category 1B and in another LLNA it showed EC3 value of 1.3% suggesting Category 1A. However, in the second LLNA only two concentration levels were available for analysis precluding a dose-response assessment. Overall, the DS considers Category 1 as appropriate without sub-categorisation.

A3.5.3 Conclusion on classification and labelling for skin sensitisation
Based on the available data, the DS proposes Category 1 for skin sensitisation for sodium pyrithione according to the CLP criteria. The corresponding hazard statement is H317: May cause an allergic skin reaction.

A3.5.4 Overall conclusion on skin sensitisation related to risk assessment
Not applicable for the CLH report.

A.3.6. Respiratory sensitisation

Table A.50 Summary table of animal data on respiratory sensitisation
No animal data is available.

Table A.51 Summary table of human data on respiratory sensitisation
No human data is available.

Table A.52 Summary table of other studies relevant for respiratory sensitisation
No other data is available.

A3.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation
No relevant data is available.

A3.6.2 Comparison with the CLP criteria
Not applicable.

A3.6.3 Conclusion on classification and labelling for respiratory sensitisation
In the absence of any relevant data, the hazard class is not assessed in this dossier.

A3.6.4 Overall conclusion on respiratory sensitisation related to risk assessment
Not applicable for the CLH report.

A.3.7. Repeated dose toxicity/STOT RE

Note: Pyrithione has been shown to cause blindness in dogs through a species-specific mechanism (degradation and atrophy of tapetum lucidum together with choroidal inflammation and retinal detachment). Therefore, for animal welfare reasons no dog studies were submitted for the review of sodium pyrithione as a biocidal active substance.

A.3.7.1. Short term repeated dose toxicity

A3.7.1.1 Short-term oral toxicity

Table A.53 Summary table of oral short-term animal studies (usually 28-day studies)

<table>
<tr><th colspan="7">Summary table of oral short-term animal studies (usually 28-day studies)</th></tr>
<tr><td>Method, Duration of study, Route of exposure (gavage, in diet, other) Guideline, GLP status, Reliability, Key/supportive study</td><td>Species, Strain, Sex, No/group</td><td>Test substance (including purity), Vehicle, Dose levels, Duration of exposure</td><td>NOAEL, LOAEL</td><td>Results (all dose levels including severity and magnitude of all effects, including also target organs)</td><td>Remarks (e.g. major deviations)</td><td>Reference</td></tr>
<tr><td>Range finding study for the one-year study,

28-days,

Oral gavage,

Not according to any guideline,

According to GLP,
Reliability: 3</td><td>Cynomolgus monkey,
Macaca fascicularis,
1/sex/group</td><td>40% aqueous solution of sodium pyrithione (<50% a.i. in aqueous solution),

Deionized water,

Dose levels in mg/kg bw/day:
<table><tr><td></td><td>Days 1-16</td><td>Days 17-23</td><td>Days 24-28</td></tr><tr><td>Group 1</td><td>1</td><td>100</td><td>400</td></tr><tr><td>Group 2</td><td>5</td><td>5</td><td>1200</td></tr><tr><td>Group 3</td><td>15</td><td>15</td><td>15</td></tr><tr><td>Group 4</td><td>50</td><td>200</td><td>800</td></tr></table></td><td>NOAEL: 5 mg/kg

LOAEL: 15 mg/kg</td><td>Emesis was noted in 15 mg/kg, 400 mg/kg and above groups during the first hour post-dose on several days in week 4. Emesis was also noted three hours post-dose on day 14 for one animal 15 mg/kg group. The presence of gallop heart rhythm was seen at 1/100/400 mg/kg doses, but not at higher doses.
One female died in the 5/1200 dose group at day 28 at the end of the 1200 mg/kg dosing regiment. Gross pathology of the liver of one male at 15 and one female at 800 mg/kg/day showed nodules, but the significance of the lesion was unknown.</td><td>The study is not reliable as the same animal got three different doses over the time and therefore the total effect of every single dose could not be evaluated. Moreover, in guideline studies many more parameters are evaluated (e.g. blood analysis) than what has been done in this study. The emesis also makes it difficult to know what dose the animals really were exposed to.</td><td>Doc IIIA A6.4.1/03

Year: 1988

(unpublished)</td></tr>
</table>

Table A.54 Summary table of human data on short-term oral toxicity

No human data is available.

A3.7.1.2 Short-term dermal toxicity
Table A.55 Summary table of dermal short-term animal studies (usually 28-day studies)
No animal data is available.

Table A.56 Summary table of human data on short-term dermal toxicity
No human data is available.

A3.7.1.3 Short-term inhalation toxicity
Table A.57 Summary table of inhalatory short-term animal studies (usually 28-day studies)
No animal data is available.

Table A.58 Summary table of human data on short-term inhalation toxicity
No human data is available.

A3.7.1.4 Overall conclusion on short-term repeated dose toxicity related risk assessment
Not applicable for the CLH report.

A.3.7.2. Sub-chronic repeated dose toxicity

A3.7.2.1 Sub-chronic oral toxicity
Table A.59 Summary table of oral sub-chronic animal studies (usually 90-day studies)

Summary table of oral sub-chronic animal studies (usually 90-day studies)						
Method, Duration of study, Route of exposure (gavage, in diet, other), Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/ group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	NOAEL, LOAEL	Results (all dose levels including severity and magnitude of all effects, including also target organs)	Remarks (e.g. major deviations)	Reference
Repeated dose toxicity study, 90-day, Oral gavage,	Rat, Sprague -Dawley Crl:CD® BR, 10/sex/ group	Sodium pyrithione (purity not specified; 40% solution in distilled water was reported as purity by the	NOAEL: 0.5 mg/kg LOAEL: 2.5 mg/kg	**High dose**: ↑ salivation, ↑ water consumption, (↑ hunched posture, increased respiratory rate and tiptoe gait in one female),	The clinical observations in one high dosed female may have been caused by the characteristic pyrithione neuropathy. Treatment related changes, i.e.	Doc IIIA A6.4.1/01 Year: 1997 (unpublish

US EPA guideline 40 CFR 798.2650, GLP: Yes, Reliability: 1, Key study		applicant), Distilled water, 0; 0.1; 0.5; and 2.5 mg/kg bw/day		↑ liver weights and histological changes in the liver, ↑ rel. adrenal weight in females ↑ rel. heart weight in males **Mid dose:** ↑ rel. heart weight in males	hypertrophy of hepatocytes, were observed in each of the dosed groups. These effects in the liver are considered as adaptive liver changes and were not indicative of an adverse effect on health. Some changes were seen in the haematological parameters but all the individual data were within the expected normal range and a statistical increase in the severity of mononuclear cell infiltrates was observed in high dose females, the toxicological significance of which is uncertain.	ed)
Repeated dose toxicity study, 90-day, Oral gavage, US EPA guideline 40 CFR 798.2650, GLP: Yes, Reliability: 1, Key study	Rat, Sprague -Dawley Crl:CD® BR (VAF Plus), 20/sex/ group	Sodium pyrithione (purity not specified; 41.2% aqueous solution was reported as purity by the applicant), Distilled water, 0; 0.5; 2; and 8 mg/kg bw/day	NOAEL: 0.5 mg/kg LOAEL: 2.0 mg/kg	**High dose**: 10 of 20 females were killed in extremis. ↓ bw gain (by 20% compared to controls), ↓ food consumption (by 10% compared to controls), Progressive hind limb paralysis (associated with emaciation, piloerection and hunched posture) in 16/20 females and 4/20 males, ↓ hind limb grip strength and foot spread on landing, ↑ atrophy of panniculus and upper hind limb muscles **Mid dose**: Slight atrophy of upper hind limb muscles in 5/20 males and in 1/20 females, atrophy of panniculus muscles in 3/20 females.	-	Doc IIIA A6.4.1/02 Year:1988 (unpublish ed)
Repeated dose toxicity study, 90-day, Oral gavage,	Rat, Wistar (Crl:WI(Han)), 10/sex/ group	Sodium pyrithione (purity not specified; 40.8% aqueous solution),	NOAEL-males: 5 mg/kg NOAEL-females:	**High-dose**: 1 female was euthanized in extremis on day 52. It had hunched posture, uncoordinated movements, rales, salivation, lean appearance, moderate skeletal muscle atrophy with axonal degeneration.	Hearing ability was not assessed during the functional observations and grip strength was not assessed for animals in low- and mid-dose groups though a significant effect was	BPR Art. 95 dossier Year: 2015

OECD 408 (1998 version), GLP: yes, Reliability: 1 Key study		Water, 0, 0.5, 2.5, 5 mg/kg bw/day	0.5 mg/kg LOAEL-females: 2.5 mg/kg	Of the remaining females, 4 had lean appearance and 3 had hunched posture. ↑ salivation (considered to be related to possible irritancy/taste and not to be toxicologically relevant according to the study author) ↓ fore- and hind-limb grip strength in females. 23% ↓ body weight gains in females. ↑ lymphocytes and ↓ haemoglobin in males. ↑ eosinophils and plate counts in females (however, the values were within the historical control range and were considered not to be toxicologically relevant) ↑ total bilirubin and bile acids in males. ↑ sodium, ↑ chloride, ↓ urea and ↓ creatinine in females. [Except the changes in creatinine, the rest were considered to be normal variations and not to be adverse] Reduced size of the thigh muscle in all surviving females. ↑ rel. spleen and liver weights in both males and females. ↑ thyroid (abs. & rel.), thymus and kidney weights in females. ↑ rel. brain and heart weights in females were considered to be secondary to the lower terminal body weights. Atrophy of the skeletal muscle in 10/10 females (1 minimal, 5 slight, 3 moderate, 1 marked). Fat replacement of the skeletal muscle in 6/10 females (2, minimal, 4 slight). Axonal degeneration in nerve branches of the affected skeletal muscle in 4/10 females (2 minimal, 1 slight, 1 moderate). **Mid-dose**: ↑salivation (considered to be related to	seen in the high-dose group. However, these deviations were not considered to be critical as any deficiencies in hearing ability would have been evident during the arena observations and histopathological data (relevant to effects on grip strength) from mid-and high-dose females showed clear effects.	(unpublished)

				possible irritancy/taste and not to be toxicologically relevant) ↓ haemoglobin in males (within historical control range and were considered not to be toxicologically relevant) ↓ body weight gains in females during most of the treatment period (however, not always statistically significant) Increased bile acids in males but not statistically significant. Reduced sized of the thigh muscle in one female. ↑rel. liver weights in females. Atrophy of the skeletal muscle in 4/10 females (2 minimal, 1 slight, 1 moderate). Fat replacement of the skeletal muscle in 1/10 females (minimal).		

Table A.60 Summary table of human data on sub-chronic oral toxicity
No human data is available.

A3.7.2.2 Sub-chronic dermal toxicity
Table A.61 Summary table of dermal sub-chronic animal studies (usually 90-day studies)

Summary table of dermal sub-chronic animal studies (usually 90-day studies)						
Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/ group	Test substance (including purity), Vehicle, Dose levels, Surface area, Duration of exposure	NOAEL, LOAEL	Results (all dose levels including severity and magnitude of all effects, including target organs)	Remarks (e.g. major deviations)	Reference
Repeated dose toxicity study, 13-weeks, US EPA FIFRA Guideline 82-3,	Rat, Sprague-Dawley, 20/sex/group	Sodium pyrithione (purity not specified; 41.2% aqueous solution), Distilled water, 0, 5, 15 and 50 mg/kg,	NOAEL: 5 mg/kg LOAEL: 15 mg/kg	**High dose**: Emaciation (from week 4 in females), hunched posture (from week 7 in 10/20 females), stiffness of movement in the hind limbs (from week 7 in 15/20 females) and isolated incoordination or tremors in two females (weeks 6-10 in one and only week 9 for the other). One male showed emaciation.	-	Doc IIIA A6.4.2/02 Year: 1988 (unpublished)

GLP: yes, Reliability: 1, Key study		Approx. 10% of surface area, 13 weeks (7 days per week)		↓ mean body weights of males and females at termination by 9 and 17%, respectively, compared to controls. Transient ↓ in food consumption from week 3. The mean food intake of males was 9 and 8% lower during weeks 3 and 4, respectively. The mean food intake of females was 15, 12 and 8% lower during weeks 3, 4 and 5, respectively. The food intake was later similar to controls and the total food intake was within 3% of controls. Wasting of skeletal muscle in 2/20 males and in 19/20 females. ↑ rel. weights of the adrenals, brain, heart, lungs, kidneys and testes which was attributed to the decreased body weights. ↑ rel. liver weight in males and females (and in only females at mid-dose). However, because of no adverse changes in relevant clinical chemistry parameters or liver histopathology, this was considered to be physiological adaptation to the metabolism of a xenobiotic Atrophy of the upper hind limb muscles in 17/19 males and 20/20 females. Atrophy of panniculus muscle in 17/20 males and 20/20 females. Minimal atrophy of paravertebral muscles in 10/20 females. Degeneration of sciatic nerve in 10/20 females. **Mid dose**: Wasting of skeletal muscle in 3/20 females. ↑ rel. liver weight in females. Minimal atrophy of the upper hind limb muscles in 1/20 males and 17/20 females. Atrophy of panniculus muscle in 9/20 females.		

Table A.62 Summary table of human data on sub-chronic dermal toxicity
No human data is available.

A3.7.2.3 Sub-chronic inhalation toxicity
Table A.63 Summary table of inhalatory sub-chronic animal studies (usually 90-day studies)

Summary table of inhalatory sub-chronic animal studies (usually 90-day studies)						
Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/ group	Test substance (including purity), form (gas, vapour, dust, mist) and particle size (MMAD), Actual and nominal concentration, Type of administration (nose only / whole body/ head only), Duration of exposure	NOAEL, LOAEL	Results (all dose levels including severity and magnitude of all effects, including also target organs)	Remarks (e.g. major deviations)	Reference
Repeated dose toxicity study, 13 weeks, US EPA guideline 82-4, subdivision F, GLP: Yes, Reliability: 2, Key study	Rat, Sprague-Dawley, 15/sex/dose	Sodium pyrithione (purity not specified; 40% aqueous solution), Aerosol, MMAD [µm] ± geometric standard deviation [µm] Low-dose group: 1.3 ± 1.81 Mid-dose group: 1.1 ± 1.94 High-dose group: 1.4 ± 2.09, Nominal conc.: 0, 0.0021, 0.0033, 0.01 mg/L (in the high dose group the conc. was increased to 0.0237 mg/L after 6 weeks), Actual conc.: 0, 0.00046, 0.0011, 0.0038 mg/L (after 6 weeks the conc. in the high dose group was 0.0081 mg/L), Whole body exposure, 13 weeks (6 h per day and	NOAEC: 0.0011 mg/L LOAEC: 0.0081 mg/L	Four females in the high dose group exhibited bilateral hind limb weakness. Those females exhibiting affects in the hind limbs also had microscopic findings of a regenerative process occurring in the skeletal muscle. In addition, females in the high dose group were observed with a 12 % decrease in bodyweight for weeks 5-13 of the study.	-	Doc IIIA A6.4.3/01 Year: 1989 (unpublished)

		5 days per week)				

Table A.64 Summary table of human data on sub-chronic inhalation toxicity
No human data is available.

A3.7.2.4 Overall conclusion on sub-chronic repeated dose toxicity related risk assessment
Not applicable for the CLH report.

A.3.7.3. Long-term repeated dose toxicity

A3.7.3.1 Long-term oral toxicity
Table A.65 Summary table of oral long-term animal studies

Summary table of oral long-term animal studies						
Method, Duration of study, Route of exposure (gavage, in diet, other), Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/ group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	NOAEL, LOAEL	Results (all dose levels including severity and magnitude of all effects, including target organs)	Remarks (e.g. major deviations)	Reference
Repeated dose toxicity study, 52 weeks, Oral gavage, US EPA Guideline 83-1, GLP: yes, Reliability: 3	Cynomolgus monkey, Macaca fascicularis, 5/sex/group	Sodium pyrithione (purity not specified; 41.41% aqueous solution was reported as purity by the applicant), Deionised water, 0, 5, 25, 150 (reduced to 75 due to toxicity observed from initiation through day 6 of week 6) mg/kg bw/day	NOAEL: 5 mg/kg bw/day, LOAEL: 25 mg/kg bw/day	↑ emesis shortly after dosing in all dose groups the frequency of which increased with increasing dose. 3 animals in the high-dose died/sacrificed in extremis (after which the dose was reduced from 150 to 75 mg/kg). Statistically significant ↓ red cell parameters (e.g. erythrocytes, haemoglobin, haematocrit) in the 25 mg/kg and 75 mg/kg groups (however, within historical control values), ↑ rel. liver and kidney weights of males in the 25 and 75 mg/kg	Nine control animals accidentally received a dose of test material, 25 mg/kg, on week 31 day 6. Animals vomited within one hour after dosing in 6 of those 9 control animals. In addition, all control animals were inadvertently administered incorrect dosage volumes of the vehicle control on day 3 of week 34. The emesis shortly after dosing makes it difficult to estimate the actual dose the animals were exposed to. ----------	Doc IIIA A6.4.1/04 Year: 1989 (unpublished)

<table>
<tr><td></td><td></td><td></td><td></td><td>groups, the rel. kidney weight of males in also 5 mg/kg was increased.

↑ rel. liver weight and abs. adrenal weight of females in 75 mg/kg group.</td><td>One out of 20 low dose animals had impaired limb function.

The terminal metabolite 2-MSP was detected in plasma of all the treated animals

<table><tr><td>Dose (mg/kg)</td><td>Mean</td><td>± S.D</td></tr><tr><td>5</td><td>1.31</td><td>0.55</td></tr><tr><td>25</td><td>4.60</td><td>3.02</td></tr><tr><td>75</td><td>7.11</td><td>3.04</td></tr></table></td><td></td></tr>
<tr><td>Combined chronic toxicity/carcinogenicity study,

104 weeks,

Oral gavage,

US EPA 83-2 (comparable to OECD 453),

GLP: yes,

Reliability: 2</td><td>Rat
Crl: CD (SD) (VAF Plus)
50/sex/dose</td><td>Sodium pyrithione (purity not specified; 41.41% aqueous solution was reported as purity by the applicant),

Water,

0, 0.5, 1.5, 5 (decreased to 3.5 after 12 weeks) mg/kg bw/day</td><td>NOAEL < 0.5 mg/kg bw based on increased incidences of hind limb muscle wastage and spinal cord nerve fibres degeneration.</td><td>Dose-related weight gain reduction in the females, hind-limb muscle wastage at the high dose in males and females, degeneration of nerve fibres in the spinal cord and sciatic nerve with associated neurogenic degeneration of skeletal muscle fibres in males and females, and an increased incidence of retinal atrophy in the high-dose female rats.

Marginally increased incidences of hind limb muscle wastage and spinal cord degeneration already occurred in males at 0.5 mg/kg bw/day (Incidence of skeletal muscle degeneration in males 2/20, 4/20, 11/20 and 12/20 for controls, 0.5, 1.5 and 3.5 mg/kg bw/day respectively). Furthermore chronic inflammation of skeletal muscle occurred in 1 animal of each treated group compared to none in controls. Incidence of nerve fibre degeneration in spinal cord for males: 14/19, 15/20, 16/20, 16/20 for controls, 0.5, 1.5 and 3.5 mg/kg bw/day respectively.</td><td>-</td><td>Doc IIIA A6.5.1/01 and A6.7/01

Year: 1991

(unpublished)</td></tr>
</table>

Combined chronic toxicity/carcinogenicity study, 104 weeks, Oral gavage, EPA OPPTS 870.4300 (comparable to OECD 453), GLP: yes, Reliability: 2	Rat Hsd: Sprague Dawley SD Control, low and medium dose: 12/sex/dose; high dose: 20/sex/dose.	Sodium pyrithione (purity not specified; 40.8% aqueous solution was reported as purity by the applicant), Distilled water, 0, 0.5, 1.4, 4 (decreased to 2.8 after 7 weeks and decreased to 2.1 for female after 9 months) mg/kg bw/day Duration of exposure: at least 104 weeks, with the exception of low dose group males, which were sacrificed during week 98	NOAEL < 0.5 based on sciatic nerve degeneration in 1/12 males	Peripheral nervous tissue (the sciatic nerve was investigated histopathologically) and skeletal muscle are the main targets of toxic action and related clinical signs such as ataxia, necropsy findings and histological changes were found in the 3 dosed groups in both sexes in a dose-related expression. Changes in relative organ to body weights occurred in several organs in females at the highest dose tested (kidneys, heart, ovaries, liver, adrenals, brain). Vascular mineralization of lungs and alveolar haemorrhage was observed histopathologically in males at the highest doses (but not statistically significant).	-	Doc IIIA A6.5.1/02 and A6.7/02 Year: 2004 (unpublished)

Table A.66 Summary table of human data on long-term oral toxicity
No human data is available.

A3.7.2.2 Long-term dermal toxicity
Table A.67 Summary table of dermal long-term animal studies
A dermal 80 weeks carcinogenicity study in mice is available for sodium pyrithione (Doc IIIA A6.7.1/03). A summary of this study is available in the Table A.75 under the section A.3.9 Carcinogenicity.

Table A.68 Summary table of human data on long-term dermal toxicity
No human data is available.

A3.7.2.3 Long-term inhalation toxicity
Table A.69 Summary table of inhalatory long-term animal studies
No animal data is available.

Table A.70 Summary table of human data on long-term inhalation toxicity
No human data is available.

A3.7.3.4 Overall conclusion on long-term repeated dose toxicity related risk assessment
Not applicable for the CLH report.

A.3.7.4. Specific target organ toxicity – repeated exposure (STOT RE)

A3.7.4.1 Short summary and overall relevance of the provided information on STOT RE
In an oral rat (Sprague-Dawley) study (Doc IIIA A6.4.1/01), salivation after test substance administration and increased water consumption were observed. Furthermore, hunched posture, increased respiratory rate and tiptoe gait was observed in one high dose (2.5 mg/kg bw/day) female which may have been caused by the characteristic pyrithione neuropathy. Increased liver weight and histological changes in the liver were detected. Treatment related changes, i.e. hypertrophy of hepatocytes, were observed in each of the dosed groups. These effects in the liver are considered as adaptive liver changes and were not indicative of an adverse effect on health. Increase in heart weight was observed in the middle (0.5 mg/kg bw/day) and high dose males. Also, increase in adrenal weight was observed in high dose males.

The 2 mg/kg bw/day (mid-dose) group animals in an another oral rat (Sprague-Dawley) study (Doc IIIA A6.4.1/02) showed slight atrophy of upper hind limb muscles (5/20 males and 1/20 females) and atrophy of panniculus muscle (3/20 females), otherwise the treatment related clinical signs were mostly confined to high-dose animals (8 mg/kg bw/day) and mainly comprised a general, progressive hind limb paralysis as seen in 16/20 females and 4/20 males. The severity of this effect was also associated with emaciation, piloerection, and hunched posture. The effects were greater in females and induced a general deterioration in the condition of 10/20 of these animals to the point that they were withdrawn from the study. High-dosed (8 mg/kg bw/day) animals were observed to also have significantly decreased body weight gain which resulted in a terminal body weight that was 20 % lower than that of the control animals. Bodyweights were unaffected in the other dose groups. Food consumption in the high dose animals was decreased by approximately 10 %. Again in the high-dose animals treatment related increases in liver and kidney weights were observed; however, the pathology for both organs was unremarkable. Microscopic findings observed mainly in the high-dose females and a few high-dose males were skeletal muscle atrophy of the upper hind limbs and subcutaneous panniculus muscle. Similar, but less severe affects, were observed in the mid-dose (2 mg/kg bw/day) animals.

In a recent 90-day repeated dose toxicity study on Wistar rats (Year: 2015; BPR Art. 95 dossier), females in mid- (2.5 mg/kg bw/day) and high-dose (5 mg/kg bw/day) groups showed skeletal muscle atrophy. The females in the high-dose group had hunched posture, lean appearance and a 23% reduced body weight gain compared to controls. The adverse effects in females included abnormal gait, statistically significant decrease in fore- and hind-limb grip strength, atrophy of the skeletal muscle along with fat replacement of myofibers and axonal degeneration. One high-dose female was euthanized in extremis on day 52. It had hunched posture,

uncoordinated movements, rales, salivation, lean appearance, moderate skeletal muscle atrophy with axonal degeneration. There were also changes in males and/or females in clinical biochemistry parameters (bilirubin, bile acids, urea, creatinine) and relative organ weights (spleen, liver, thyroid, thymus and kidney weights) which were considered to be not adverse as the findings were within historical control range or the changes in organ weights were not correlated with microscopic findings. The mid-dose females had lower body weight gains, atrophy and fat replacement of skeletal muscle. The NOAEL for males was set at 5 mg/kg bw/day (high-dose) while for females at 0.5 mg/kg bw/day (low-dose) based on skeletal muscle atrophy in mid- (2.5 mg/kg bw/day) and high-dose groups.

In a 28-day range-finding study (Doc IIIA A6.4.1/03) for the 52-week study on Cynomolgus monkey, emesis was seen with 15 mg/kg bw/day and with 400 mg/kg bw/day and above. The presence of gallop heart rhythm was seen at 1/100/400 mg/kg bw/day doses, but not at higher doses. The reliability factor was set to 3 as the same animal received three different doses over time and therefore the total effect of every single dose could not be evaluated. Moreover, in guideline studies many more parameters are evaluated (e.g. blood analysis) than what has been done in this study. The emesis also makes it difficult to know which dose the animals really were exposed to. For the first 16 days, 1 male and 1 female animal received 0, 1, 5, 15, or 50 mg/kg bw/day once daily and from day 17 to day 23 animals received 0, 100, 5, 15, or 200 mg/kg and on days 24 to 28 they received 0, 400, 1200, 15, or 800 mg/kg bw/day, respectively. One female animal died on the last day of the study at the 1200 mg/kg dose. No other signs of toxicity were observed in any of the animals.

In a one-year study on Cynomolgus monkey (Doc IIIA A6.4.1/04), the doses administered were 0, 5, 25, 150 (for the first 6 weeks which was reduced to 75 mg/kg bw/day due to overt toxicity). One female was sacrificed in extremis in the high dose group, at 6 weeks after observed thinness, cold extremities and decreased activity/prostration (reason for lowering the high dose of 150 to 75 mg/kg bw/day). One male died at week 13 and another female at week 35 in the high dose group. In the pathological examination there was no visible test article related findings in any of the animals. The only other finding was a significant decrease in red cell parameters e.g. erythrocytes, haemoglobin and haematocrit in the mid-dose (25 mg/kg bw/day) and the high-dose animals. One out of 20 animals had impaired limb function and it appeared to be reduced muscle mass. The observation was made at 3, 6, 9, and 12 months. This may be the same effect as seen in the rat studies; however as the effect was seen in the lowest dose only and in only one animal, it is likely to be fortuitous. The reliability factor was set to 3, as controls was accidently exposed at one time, and most important, the emesis makes it difficult to estimate the dose that the monkeys were really exposed to.

In the 90-d dermal toxicity study in Sprague Dawley rats (Doc IIIA A6.4.2/02), treatment related clinical signs were observed in the high-dose group (50 mg/kg bw/day), particularly in females, including emaciation, hunched posture, stiffness of movement in the hind limbs and isolated incoordination or tremors. There was marked adverse effects on body weight in the high-dose group, particularly in females. The mean body weight of males and females at termination were lower by 9 and 17%, respectively, compared to controls. Atrophy of the upper hind limb muscles was observed in 17/19 males and 20/20 females in the high-dose group. Mild atrophy of the upper hind limb muscles was observed in 1/20 males and 17/20 females in the mid-dose group (15 mg/kg bw/day). Atrophy of panniculus muscle was observed in 17/20 males and 20/20 females in the high-dose group and in 9/20 females in the mid-dose group. Moreover, mild atrophy of paravertebral muscles and degeneration of sciatic nerve was observed in 10/20 high-dose

females. The NOAEL in this study was set at the low-dose (5 mg/kg bw/day).

The most significant observation from the inhalation (whole body) study in Sprague-Dawley rats (Doc IIIA A6.4.3/01) was the observation of depressed body weights (12%) in females in the high dose group. In addition, four females in the high dose group were observed with a slight bilaterally impaired hind limb function. This might be due to oral ingestion from preening or to a systemic effect after inhalation. Those females exhibiting affects in the hind limbs also had microscopic findings of a regenerative process occurring in the skeletal muscle. The LOAEC was estimated to be 0.0081 mg/L and the NOAEC to be 0.0011 mg/L. As systemic effects were seen in the study, it was of interest to compare the inhaled exposure doses with dose used in the oral studies. Using default values for breathing rate from the TGD, the dose in mg/kg bw/day can be calculated as below.

There is no information available on inhalation absorption and therefore a default value of 100% is assumed.

Rat breathing rate = 175 mL/minute* = 10.5 L/h

Study exposure period was 6 hours/day

Rat body weight ** = 275 g = 0.275 kg

Inhaled dose at NOAEC= 0.0011 mg/L x 10.5L/h x 6 h/day / 0.275 kg = 0.25 mg/kg bw/day

Inhaled dose at LOAEC= 0.0081 mg/L x 10.5L/h x 6 h/day / 0.275 kg = 1.9 mg/kg bw/day

* (TGD Part I 2003, Appendix VI, table 6, rat M+F 90-day study)

** (TGD Part I 2003, Appendix VI, table 1, rat M+F 90-day study)

A NOAEL of 0.257 mg/kg bw/day and LOAEL of 1.9 mg/kg bw/day from the inhalation study are lower than the levels seen in the two oral 90 days studies; NOAEL 0.5 mg/kg bw/day and LOAEL 2.5 and 2 mg/kg bw/day.

Furthermore, there are two 2-year oral combined toxicity/carcinogenicity studies on rats and three pre-natal developmental toxicity (PNDT) studies (in rats via oral and dermal routes and in rabbits via dermal route).

In the first 2-year oral combined toxicity/carcinogenicity study (Doc IIIA A6.5.1/01 and A6.7/01), rats were exposed to 0.5, 1.5 and 5 (decreased to 3.5 after 12 weeks) mg NaPT/kg bw/day. Decreased body weight gain, hind limb muscle atrophy and histopathological changes in skeletal muscle, spinal cord, and eyes were observed in the high-dose group. Some, but not all of these effects were observed to a lesser degree in the mid-dose group. Marginally increased incidences of hind leg wasting and spinal cord degeneration occurred in males already at 0.5 mg/kg bw/day (the incidence of skeletal muscle degeneration in males was 2/20, 4/20, 11/20 and 12/20 for controls, 0.5, 1.5 and 3.5 mg/kg bw/day respectively). Furthermore chronic inflammation of skeletal muscle occurred in

one animal of each treated group compared to none in controls. The incidence of nerve fibre degeneration in spinal cord for males was found to be 14/19, 15/20, 16/20, 16/20 for controls, 0.5, 1.5 and 3.5 mg/kg bw/day respectively. Thus the NOAEL was found to be <0.5 mg/kg bw/day.

In the second 2-year oral combined toxicity/carcinogenicity study (Doc IIIA A6.5.1/02 and A6.7/02), rats were exposed to 0.5, 1.4, 4 (decreased to 2.8 after 7 weeks and decreased to 2.1 for females after 9 months) mg/kg bw/day. Signs of toxicity such as ataxia, decreased muscle tone and emaciation were seen in a few animals of the mid-dose group and in some males and most females in the high-dose group. There were treatment related degenerative changes of the sciatic nerve and skeletal muscle in all treatment groups. In addition, reduced body weight was noted in low and high-dose males and in mid- and high- dose females when compared to controls. Low-dose males were sacrificed during week 97 due to the high mortality observed in this group. Mortality of the mid- and high-dose females (1.5, 2.1 mg/kg bw/day) was also higher than controls. However, there were no significant differences in pathology between controls and treated animals. A gastric reactive change was observed at 2.8 mg/kg bw/day in male rats only while high-dosed females had significantly decreased heart weights compared to controls. As sciatic nerve degeneration occurred already at the lowest dose in males (in one animal only but in none of the controls) the NOAEL was set to < 0.5 mg/kg bw/day.

In a 2-generation oral reproductive toxicity study (Doc IIIA A6.8.2/01), rats (Crl:CD(SD)BR) were exposed to 0.5, 1.5 and 3.5 (4.5 during the first three weeks) mg NaPT/kg bw/day. One P and two F1 females in the high-dose group were humanely sacrificed and showed hind limb paralysis or impairment of hind limb movement. The high-dose P and F1 animals had reduction in body weight gain, atrophy of hind limb muscle fibres. In the mid-dose group the adverse effects were limited to atrophy of the hind limb muscles in a few P females.

In another 2-generation oral reproductive toxicity study (Doc IIIA A6.8.2/02), rats (Hsd: Sprague Dawley) were exposed to 0.7, 1.4 and 2.8 mg NaPT/kg bw/day. The high-dose P and F1 animals had reduction in body weight gain. The histopathological examinations in this study did not include previously identified target organs: skeletal muscle, sciatic nerve and spinal cord.

In a PNDT study in rats via oral route (Doc IIIA A6.8.1/04), the dams in the high-dose group (4 mg/kg bw/day) had decreased food consumption and 56% reduced body weight gain compared to controls, difficulty in movement and impairment of hind limbs. In a PNDT study in rats via dermal route (Doc IIIA A6.8.1/05), the dams in the high-dose group (7 mg/kg bw/day) had increased mortality (20%), 84% reduced body weight gain compared to controls, decreased thymus weight and fore- and hind-limb weakness. In a PNDT study in rabbits via dermal route (Doc IIIA A6.8.1/06), the high-dose group (5 mg/kg bw/day) does had 39% reduced body weight gain compared to control.

Table A.71 Effects and corresponding guidance values to assist classification for STOT RE.

Study reference	Target organ effect(s) (all	Effective dose (mg/kg bw/d)	Length of exposure	Guidance value/extrapolated	Classification supported by

	significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed)			guidance value when extrapolated to the exposure duration other than 90 days	the study (Cat 1, Cat 2, NC)
Doc IIIA A6.4.1/01 Year: 1997 RDT study in rats via oral route	↑ salivation, ↑ hunched posture, increased respiratory rate and tiptoe gait in female	2.5	90-d	≤ 10	Cat 1
Doc IIIA A6.4.1/02 Year: 1988 RDT study in rats via oral route	50% female mortality, 20% ↓ bw gain, hind limb and panniculus muscles effects	8	90-d	≤ 10	Cat 1
	Hind limb and panniculus muscles effects	2	90-d	≤ 10	Cat 1
BPR Art. 95 dossier Year: 2015 RDT study in rats via oral route	5% mortality (only at 5 mg/kg), ↑ salivation, 23% ↓ bw gain, hind limb and skeletal muscle effects	2.5 and 5	90-d	≤ 10	Cat 1
Doc IIIA A6.4.2/02 Year: 1988 RDT study in rats via dermal route	Hind limb, panniculus and skeletal muscle effects	15	90-d	≤ 20	Cat 1
	↓ mean bw of males and females at termination by 9 and 17%,	50	90-d	10 < C ≤ 100	Cat 2

	respectively, compared to controls, degeneration of sciatic nerve				
Doc IIIA A6.4.3/01 Year: 1989 RDT study rats via inhalation route	Hind limb and skeletal muscle effects	2.8 (mg/kg bw/day)* (0.0081 mg/L)	90-d	≤ 7 (mg/kg bw/day)* (0.02 mg/L/6h/day)	Cat 1
Doc IIIA A6.5.1/01 and A6.7/01 Year: 1991 Combined chronic toxicity/carcinogenicity study in rats oral route	Hind limb muscle wastage and spinal cord nerve fibres degeneration	0.5	104-w	≤ 1.25	Cat 1
	Sciatic nerve degeneration and retinal atrophy	3.5	104-w	1.25 < C ≤ 12.5	Cat 2
Doc IIIA A6.5.1/02 and A6.7/02 Year: 2004 Combined chronic toxicity/carcinogenicity study in rats oral route	Sciatic nerve degeneration	0.5	104-w	≤ 1.25	Cat 1
	Skeletal muscle effects, mortality (66% compared to 55% in controls)	1.4	104-w	1.25 < C ≤ 12.5	Cat 2
	Mortality (70% compared to 55% in controls)	4 (decreased to 2.8 after 7 weeks and to 2.1 for females after 9 months)	104-w	1.25 < C ≤ 12.5	Cat 2
Doc IIIA A6.8.1/04 PNDT study in rats via oral route	56% ↓ bw gain, difficulty in movement, impairment of	4	14-d	60	Cat 1

	hind limbs				
Doc IIIA A6.8.1/05 PNDT study in rats via dermal route	20% mortality, 84% ↓ bw gain, ↓ thymus weight, fore- and hind-limb weakness	7	10-d	180	Cat 1
Doc IIIA A6.8.1/06 PNDT study in rabbits via dermal route	39% ↓ bw gain	5	14-d	120	Cat 1

* Recalculated using the values: inhalation absorption = 100%; rat breathing rate = 10.5 L/h; study exposure period: 6 h/day; rat body weight = 0.185 kg.

A3.7.4.2 Comparison with the CLP criteria

Substances are classified in STOT RE Category 1 based on evidence of significant toxicity in humans or where there is evidence from studies in experimental animals that they can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. For classification in Category 1, either reliable good quality human data (evidence from human cases or epidemiological studies) or animal data (observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were observed at generally low exposure concentrations) is required. Annex I, Section 3.9.2.9.6 of the CLP Regulation provides a 'guidance value' of ≤ 10 mg/kg bw/d from a 90-day rat study via oral route to assist in Category 1 classification. It can be used as a basis to extrapolate equivalent guidance value for toxicity studies of greater or lesser duration. For a 28-day study it is increased by a factor of three (i.e. ≤ 30 mg/kg bw/d) and for a 365-d study it may be decreased by a factor of four (i.e. ≤ 2.5 mg/kg bw/d) to assist in Category 1 classification.

Substances are classified in STOT RE Category 2 based on evidence from studies in experimental animals that they can be presumed to have the potential to be harmful to human health following repeated exposure. For classification in Category 2, animal data (observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were observed at generally moderate exposure concentrations) is required. Annex I, Section 3.9.2.9.7 of the CLP Regulation provides a 'guidance value' of 10-100 mg/kg bw/d from a 90-day rat study via oral route to assist in Category 2 classification. For a 28-day study it is increased by a factor of three (i.e. ≤ 300 mg/kg bw/d) and for a 365-d study it may be decreased by a factor of four (i.e. ≤ 25 mg/kg bw/d) to assist in Category 1 classification.

The main effects of NaPT observed in rats after oral exposure were mortality, hind limb weakness/paralysis, skeletal muscle effects

and reduced body weight gain. According to a published study by Knox et al (2008)[10] hind limb effects caused by NaPT, are due to a reduced rate of axoplasmic transport and the resulting accumulation of tubulovesicular profiles at the distal nerve terminals of motor neurons leading to failure of synaptic transmission at neuro-muscular junctions. The study showed that NaPT evoked increased Ca^{2+} levels in motor neurons of both rats and monkeys, but with a significant difference in sensitivity between the two species. The EC50 for the increase in Ca^{2+} levels in the monkey motor neuron was 30 times higher that of the value in rats. The data also showed that there was a clear threshold for the Ca^{2+} increase in both species and that reversal of the effects was only partially successful in the majority of cases. The relevance of the hind limb effects to humans was questioned by the applicant; however the RMS considers this data to indicate that there is merely a difference in sensitivity between rodents and primates; furthermore, Ca^{2+} channels are ubiquitous in the human body and play important roles in many cell types and effects on these are thus considered relevant also for humans, although it is recognized that Ca^{2+} channels may differ among species.

There was a lack of relevant histopathological findings on major organs in all of the performed studies; a possible explanation could be the effect of pyrithione on intracellular Ca^{2+} levels which is known to be toxic in high concentrations and could probably result in sudden death of the animals once the Ca^{2+} gradient has collapsed in vital organs such as the heart.

According to the Industry the proposed mode of action of pyrithiones is Krebs cycle arrest via aconitase inhibition which leads to an impaired energy production on cellular level with numerous downstream effects at physiological processes of an organism. Food-conversion, which correlates food consumption to the body weight gain during a defined period, is one of the downstream effects. However, it should be stated that the mechanism of action of sodium pyrithione has not yet been fully elucidated.

The following significant and/or severe toxic effects that are of relevance to human health were consistently observed in several studies (summarised in Table A.72 above) on rats via oral route at low exposure concentrations and warrant STOT RE Category 1 classification: mortality and effects on neuromuscular system (sciatic nerve degeneration, effects on hind limb and skeletal muscles).

Mortality and effects on neuromuscular system warranting STOT RE Category 1 were also observed in studies on rats and rabbits via dermal route.

Effects on neuromuscular system warranting STOT RE Category 1 were observed in a study on rats also via inhalation route.

A3.7.4.3 Conclusion on classification and labelling for STOT RE
Based on the studies presented above, classification as STOT RE 1; H372 (mortality, neuromuscular system) is proposed for sodium pyrithione according to the CLP criteria. It is proposed not to specify the route of exposure as mortality was observed by two routes (oral and dermal) and effects on neuromuscular system were observed by three routes (oral, dermal and inhalation).

[10] Knox, R. J., Keen, K. L., Luchansky, L, Terasawa, E., Freyer, H., Barbee, S. J., Kaczmarek, L. K.: Comparative effects of sodium pyrithione evoked intracellular calcium elevation in rodent and primate ventral horn motor neurons. Biochemical and Biophysical Research Communications. 2008, 366: 48-53.

A.3.8. Genotoxicity / Germ cell mutagenicity

A.3.8.1. In vitro

Table A.72 Summary table of in vitro genotoxicity studies

Summary table of in vitro genotoxicity studies					
Method, Guideline, GLP status, Reliability, Key/supportive study	Test substance (including purity), Vehicle, Doses	Relevant information about the study (e.g. organism (e.g. bacteria), cell type, strains)	Results (including cytotoxicity and +/-S9 mix)	Remarks (e.g. major deviations)	Reference
Bacterial reverse mutation test, OECD 471 (1997), GLP: yes, Reliability: 1, Key study	Sodium pyrithione (40.8% aqueous solution; purity not specified), Distilled water, Experiment 1: 0; 6.25; 12.5; 25; 50; 100 µg/plate; Experiment 2, strains TA 1535, TA 98, TA 100, TA 102: 0; 3.13; 6.25; 12.5; 25; 50; 100 µg/plate Experiment 2, strain TA1537: 0; 1.56; 3.13; 6.25; 12.5; 25; 50 µg/plate	*S. typhimurium*: TA 1535, TA 1537, TA 98, TA 100, TA 102	Cytotoxicity: Yes +S9-mix: Negative - S9-mix: Negative	-	Doc IIIA A6.6.1/01 Year: 2002 (unpublished)
Bacterial reverse mutation test, OECD 471, GLP: yes, Reliability: 1,	Sodium pyrithione Water, Experiment 1 and 2 (direct plate incorporation method): TA100, TA1535, TA98 and WP_2uvrA (+/-S9-mix): 1.5, 5, 15, 50, 150 and 500 µg/plate.	*S. typhimurium*: TA 1535, TA 1537, TA 98, and TA 100 *E. coli*: WP_2uvrA	Cytotoxicity: Yes +S9-mix: Negative - S9-mix: Negative	The DS does not have access to the full study report.	REACH registration dossier, JS member, Opt-out Year: 2000

Key study	TA1537 (+/- S9-mix): 0.5, 1.5, 5, 15, 50 and 150 µg/plate.				
Bacterial reverse mutation test, OECD 471, GLP: yes, Reliability: 1, Key study	Sodium pyrithione (40.8% aqueous solution; purity not specified), Water, Experiment 1: TA1535, TA1537, TA98 (+/- S9-mix): 3, 10, 33, 100, 333 and 666 µg/plate. TA 100 and WP_2uvrA (+/- S9 mix): 3, 10, 33, 100, 333, 1000, 3330 and 5000 µg/plate. Experiment 2: TA1535, TA1537, TA98 and TA100 (- S9-mix): 1 to 333 µg/plate; WP_2uvrA (+/- S9-mix): 1 to 1000 µg/plate; TA1535 (+ S9-mix): 1 to 333 µg/plate; TA1537, TA98 and TA100 (+ S9-mix): 3 to 666 µg/plate.	*S. typhimurium*: TA 1535, TA 1537, TA 98, and TA 100 *E. coli*: WP_2uvrA	Cytotoxicity: Yes + S9-mix: Negative - S9-mix: Negative	-	BPR Art. 95 dossier Year: 2014 (unpublished)
Chromosomal aberration test in mammalian cells, OECD 473, GLP: yes, Reliability: 1, Key study	Sodium pyrithione (40.8% aqueous solution; purity not specified), Distilled water, Concentrations used: 0; 0.313; 0.625; 1.25; 2.50; 5; 10; 20; 40; 80 µg/mL Concentrations selected and scored for chromosomal aberrations: 0; 20; 40; 80 µg/mL	Chinese hamster lung fibroblasts (V79 cell line)	Cytotoxicity: - S9-mix: 80 µg/mL: 64 %; 0.313 – 40 µg/mL: 25 % – 38 %. + S9-mix: 80 µg/mL: 89 %; 0.313 – 40 µg/mL: 66 % - 92 %. +S9-mix: Positive (40; 80 µg/mL) - S9-mix: Positive (20; 40; 80 µg/mL)	-	Doc IIIA A6.6.2/01 Year: 2002 (unpublished)

<table>
<tr>
<td>Gene mutation test in mammalian cells,

OECD 476,

GLP: yes,

Reliability: 1,

Key study</td>
<td>Sodium pyrithione (40.8% aqueous solution; purity not specified),

Distilled water,

<table>
<tr><th>Assay no.</th><th>S9-mix</th><th>Dose levels (µg/mL)</th></tr>
<tr><td>1</td><td>-</td><td>1250; 938; 625; 313; 156; 78.1</td></tr>
<tr><td>1</td><td>+</td><td>313; 234; 156; 78.1; 39.1; 19.5</td></tr>
<tr><td>2</td><td>-</td><td>1875; 1250; 833; 556; 370; 247</td></tr>
<tr><td>2</td><td>+</td><td>470; 313; 209; 139; 92.8; 61.9</td></tr>
</table>
</td>
<td>Chinese hamster V79 cells.</td>
<td>Cytotoxicity: Yes

+ S9-mix: Negative
- S9-mix: Negative</td>
<td>-</td>
<td>Doc IIIA A6.6.3/01

Year: 2002

(unpublished)</td>
</tr>
<tr>
<td>Gene mutation test in mammalian cells,

OECD 476,

GLP: yes,

Reliability: 1,

Key study</td>
<td>Sodium pyrithione (41.4% aqueous solution; purity not specified),

Distilled water,

<table>
<tr><th>Assay no.</th><th>S9-mix</th><th>Dose levels (µg/mL)</th></tr>
<tr><td>1</td><td>-</td><td>0.0414; 0.0828; 0.124; 0.166; 0.207; 0.311; 0.414</td></tr>
<tr><td>1</td><td>+</td><td>4.14; 10.4; 20.7; 41.4; 62.1; 82.8; 103.5</td></tr>
<tr><td>2</td><td>-</td><td>0.005; 0.01; 0.02; 0.035; 0.05; 0.1; 0.2; 0.35; 0.5</td></tr>
<tr><td>2</td><td>+</td><td>0.5; 1.0; 2.5.0; 5.0; 10.0; 25.0; 50.0; 75.0; 100.0</td></tr>
</table>
</td>
<td>Chinese hamster ovary cells</td>
<td>Cytotoxicity: Yes

+ S9-mix: Negative
- S9-mix: Negative</td>
<td>Assay 1 was deemed too cytotoxic and was terminated.</td>
<td>Doc IIIA A6.6.3/02

Year: 1987

(unpublished)</td>
</tr>
</table>

Unscheduled DNA synthesis test in mammalian cells, US EPA 84-4, GLP: yes, Reliability: 2, Supporting study	Sodium pyrithione (41.4% aqueous solution; purity not specified), Deionized water, Calculated concentration: 7.10, 22, 71 and 220 ng/ml	Rat hepatocytes	Cytotoxicity: Yes (220 ng/ml) Result: Negative	Deviations: The study was similar to OECD 482 with the following exceptions: (i): CO2 concentration was not specified (ii): Dose-response relationship was not analysed (iii) No statistical evaluation was made	Doc IIIA A6.6.7/01 Year: 1987 (unpublished)

Table A.73(a)(i) Chromosomal aberration test in mammalian cells: Chromosomal Analysis: without metabolic activation (**Doc IIIA A6.6.2/01**)

		control	low dose **20 µg/mL**	mid dose **40 µg/mL**	high dose **80 µg/mL**
cytotoxicity (reduction of the number of viable cells to xx % of negative control value)		n.a.	64 %	25 %	29 %
Aberrations per 100 cells					
gaps		1.0	9.5	4.0	16.0
chromatid aberrations	breaks	0	8.0	3.5	32.0
	interchanges	0	3.0	2.0	9.0
isochromatid aberrations	breaks	0	0	0	0
	interchanges	0	0.5	0	0

		control	low dose **20 µg/mL**	mid dose **40 µg/mL**	high dose **80 µg/mL**
others	heavily damaged cells/100 cells (>5 aberrations/cell)	0	1.0	0.5	6.5
mitotic index		N.a.	N.a.	N.a.	N.a.
polyploidy		0	0	0	0
endo reduplication		0	0	0	0

Table A.73(a)(ii) Chromosomal aberration test in mammalian cells: Chromosomal Analysis: with metabolic activation (**Doc IIIA A6.6.2/01**)

		control	low dose **20 µg/mL**	mid dose **40 µg/mL**	high dose **80 µg/mL**
cytotoxicity (reduction of the number of viable cells to xx % of negative control value)		n.a.	89 %	66 %	66 %
Aberrations per 100 cells					
gaps		1.5	2.5	9.0	10.5
chromatid aberrations	breaks	0.5	0	8.5	11.5
	interchanges	0	0	2.0	1.5
isochromatid aberrations	breaks	0	0	0	0
	interchanges	0	0	0	0
others	heavily damaged cells/100 cells (>5 aberrations/cell)	0	0	3.0	0.5
mitotic index		N.a.	N.a.	N.a.	N.a.
polyploidy		0	0	0	0
endo reduplication		0	0	0	0

Table A.73(b)(i) Gene mutation test in mammalian cells: Assay 1 results (**Doc IIIA A6.6.3/01**)

Concentration [µg a.s./mL]	Number of plate counts (means)		Percentage survival	
	— S9	+ S9	— S9	+ S9
0	177	184	100	100

Concentration [µg a.s./mL]	Number of plate counts (means)		Percentage survival	
19.5	-	163	-	89
39.1	-	155	-	84
78.1	168	127	96	69
156	148	108	84	59
313	130	106	74	57
625	116	73	66	39
938	108	-	61	-
1250	73	-	42	-

Table A.73(b)(ii) Gene mutation test in mammalian cells: Assay 2 results (**Doc IIIA A6.6.3/01**)

Concentration [µg a.s./mL]	Number of plate counts (means)		Percentage survival	
	— S9	+ S9	— S9	+ S9
0	168	158	100	100
61.9	-	157	-	99
92.8	-	152	-	96
139	-	159	-	101
209	-	140	-	78
247	118	-	70	-
313	-	85	-	54
370	123	-	73	-
470	-	84	-	53
556	100	-	59	-
833	56	-	33	-
1250	35	-	21	-
1875	-	-	0	-

Table A.73(c)(i) Gene mutation test in mammalian cells: Assay 2 results (**Doc IIIA A6.6.3/02**)

Concentration [µg/mL]	Mutant Frequency (average)	Percentage survival	Conc (µg/mL)	Mutant Frequency (average)	Percentage survival
	— S9	— S9		+ S9	+ S9
0	1.6	100	0	1.6	100
0.005	10.5	91	0.5	9.8	55.55

Concentration [µg/mL]	Mutant Frequency (average)	Percentage survival	Conc (µg/mL)	Mutant Frequency (average)	Percentage survival
	— S9	— S9		+ S9	+ S9
0.01	4.0	93.2	1.0	1.0	22.15
0.02	2.7	82.7	2.5	2.6	12.55
0.35	5.0	42.0	5.0	<1.2	11.65
0.05	24.4	16.2	10.0	<1.2	13.05
0.1	<1.4	4.7	25.0	-	0.35
0.2, 0.35, 0.5	-	-	50, 75, 100	-	-

Table A.73(d)(i) Unscheduled DNA synthesis in mammalian cells: audioradiographic analysis of DNA Repair (**Doc IIIA A6.6.7/01**)

Treatment	Nominal concentration	Calculated concentration	Analysed concentration	Net Nuclear Grains Triplicate Cultures	Cytotoxicity
Vehicle Control dH_2O	-	-	-	-14.5 ± 5.7	-
Positive Control 2AAF	1×10^{-7} M	-	-	19.2 ± 9.2	-
NaPT	16.7 ng/ml	7.10 ng/ml	-	-17.2 ± 5.7	-
NaPT	50.0 ng/ml	22.0 ng/ml	-	-14.3 ± 7.1	-
NaPT	167 ng/ml	71.0 ng/ml	80 ng/ml	-12.5 ± 6.3	-
NaPT	500 ng/ml	220 mg/ml	300 ng/ml	-7.5 ± 6.3	+

A.3.8.2. In vivo

Table A.73 Summary table of in vivo genotoxicity studies

Summary table of in vivo genotoxicity studies					
Method, duration of study, Guideline, GLP status, Reliability, Key/supportive	Test substance (including purity), Vehicle, Doses	Relevant information about the study (e.g. species and strain, sex, no per group, route, frequency of application, sampling times, duration of	Main effects, Observations (specify regarding dose and sampling time)	Remarks (e.g. major deviations)	Reference

study		exposure)			
Micronucleus test, OECD 474, GLP: yes, Reliability: 1, Key study	Sodium pyrithione (purity: <95%), Deionised water, 400, 482, and 580 mg/kg	Mouse, Crl:NMRI BR 5/sex/dose/sampling time Oral gavage, one application Sampling times: 24 and 48 hrs post dose	Test material was bioavailable (one mortality and convulsions in a male and a female of the high-dose group) Result: Negative (no statistically significant increase in amounts of micronucleated polychromatic erythrocytes at any dose compared to negative controls at 24 or 48 hours post-treatment)	-	Doc IIIA A6.6.4/01 Year: 2001 (unpublished)
Micronucleus test, OECD 474, GLP: yes, Reliability: 1, Key study	Sodium pyrithione (41.4% aqueous solution; purity not reported), Distilled water 238 mg/kg	Mouse, CD-1 5/sex/dose/sampling time Intraperitoneal, one application Sampling times: 30, 48 and 72 hrs post dose	Test material was bioavailable (clinical signs observed in all treated animals) Result: Negative (no statistically significant increase in amounts of micronucleated polychromatic erythrocytes compared to vehicle controls at 30, 48 or 72 hours post-treatment)	-	Doc IIIA A6.6.4/02 Year: 1987 (unpublished)
Combined micronucleus test and comet assay, OECD 474 + OECD 489, GLP: yes, Reliability: 1 Key study	Sodium pyrithione (40.8% aqueous solution; purity not reported) Water, 37.5, 75 and 150 mg/kg	Rat, Wistar Han, 5 males/group (+3 additional in high dose group) Oral gavage application for 3 consecutive days Sampling times: 3-4 hrs after the last dose	Test material was bioavailable (Clinical signs in high-dose group after the second and third dose) Micronucleus test result: Negative (no statistically significant increase in amounts of micronucleated polychromatic erythrocytes compared to vehicle controls) Comet assay result: Negative (no biologically relevant increase in the mean Tail Intensity (%) in	In the comet assay, no statistically significant DNA damage was noted at any of the doses in the liver cells and at low- and mid-dose in duodenum cells. At high-dose, there was statistically significant increase in DNA damage in duodenum cells in	BPR Art. 95 dossier Year: 2015 (unpublished)

		Bone marrow sampled for micronucleus analysis Liver and duodenum examined in comet assay (duodenum was examined in two experiments)	liver and duodenum cells)	one out of two experiments. However, the histopathology of duodenum at this dose showed no adverse effects.	

Table A.74(a)(i) Micronucleus test in Crl:NMRI BR mice: results for males (**Doc IIIA A6.6.4/01**)

		control group		low dose 400 mg/kg			mid dose 482 mg/kg			high dose 580 mg/kg		
Number of cells (polychromatic erythrocytes) evaluated		2000		2000			2000			2000		
Sampling time (h)		24	48	24	-	-	24	-	-	24	48	-
Percentage of erythrocytes	normochromatic	50.5	60.1	55.7	-	-	54.4	-	-	49.3	50.6	-
	polychromatic	55.9	57.5	50.6	-	-	52.0	-	-	48.4	43.0	-
	polychromatic with micronuclei	1.20	1.80	1.80	-	-	1.60	-	-	0.96	1.40	-
Ratio of erythrocytes	polychromatic / normochromatic	1.24	1.37	1.10	-	-	1.10	-	-	0.78	1.70	-
	polychromatic with micronuclei / normochromatic	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

n.r.: not reported

Table A.74(a)(ii) Micronucleus test in Crl:NMRI BR mice: results for females (**Doc IIIA A6.6.4/01**)

		control group		low dose 400 mg/kg			mid dose 482 mg/kg			high dose 580 mg/kg		
Number of cells (polychromatic erythrocytes) evaluated		2000		2000			2000			2000		
Sampling time (h)		24	48	24	-	-	24	-	-	24	48	-
Percentage of erythrocytes	normochromatic	57.6	51.3	56.2	-	-	49.0	-	-	54.1	44.5	-
	polychromatic	55.6	54.1	48.7	-	-	51.6	-	-	54.2	52.2	-
	polychromatic with micronuclei	1.50	2.10	3.00	-	-	1.50	-	-	1.00	1.50	-
Ratio of erythrocytes	polychromatic / normochromatic	1.30	1.30	0.96	-	-	1.10	-	-	1.21	1.13	-
	polychromatic with micronuclei / normochromatic	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

n.r.: not reported

Table A.74(b)(i) Micronucleus test in CD-1 mice: Micronucleated PCE/1000 Polychromatic Erythrocytes/Animal (**Doc IIIA A6.6.4/02**)

Animal Number	Control		NaPT (238 mg/kg)		
Male	dH20 (48 hr)	TEM (30 hr)	30 h	48 h	72 h
1	0	68	0	3	0
2	1	58	1	0	1
3	0	59	1	0	1
4	0	54	1	1	4
5	2	90	1	2	1
Female					
6	2	74	0	1	3
7	2	61	2	2	0
8	1	39	1	0	1
9	1	31	1	0	1
10	0	63	1	1	0
Mean +/- SD	0.9+/-0.88	59.7+/-16.64	0.9+/-0.57	1+/-1.05	1.2+/-1.32
t value	-	11.158	0	0.23	0.6

Table A.74(b)(ii) Micronucleus test in CD-1 mice: Ratio of PCE to NCE in 1000 Erythrocytes (**Doc IIIA A6.6.4/02**)

Animal Number	Control		NaPT (238 mg/kg)		
Male	dH20 (48 hr)	TEM (30 hr)	30 h	48 h	72 h
1	1.833	0.969	1.5	1.222	1.558
2	2.39	1.123	1.433	0.848	1.488
3	1.809	0.852	1.985	2.279	1.262
4	2.155	1.457	1.825	1.463	1.667
5	1.571	1	1.165	1.681	1.564
Female					
6	1.907	1.494	1.833	1.994	1.283
7	1.475	0.931	2.425	1.717	1.155
8	1.375	1.203	3.032	2.663	1.008
9	2.195	1.545	1.695	2.484	1.222
10	1.681	1.342	2.021	2.155	1.915

Mean +/- SD	1.84+/-0.33	1.19+/-0.25	1.89+/-0.53	1.85+/-0.57	1.41+/-0.27
t value	-	4.955	0.06	0.272	3.19

Table A.74(c)(i) Combined micronucleus test and comet assay in rats: Mean number of micronucleated polychromatic erythrocytes and ratio of polychromatic/normochromatic erythrocytes (BPR Art. 95 dossier, 2015)

Group	Treatment	Dose (mg/kg body weight)	Number of micronucleated polychromatic erythrocytes (mean ± S.D.) [1,2]	Ratio polychromatic/ normochromatic erythrocytes (mean ± S.D.) [1,3]
A	Vehicle control	0	2.2 ±1.6	1.73 ±0.27
B	Sodium pyrithione	150	2.8 ±1.9	1.40 ±0.34
C	Sodium pyrithione	75	3.2 ±0.4	1.30 ±0.33
D	Sodium pyrithione	37.5	2.4 ±2.1	1.43 ±0.19
F	CP	20	43.6 ±6.8 [4]	0.78 ±0.29

Vehicle control = Elix water
CP = Cyclophosphamide.
(1) Five animals per treatment group.
(2) At least 4000 polychromatic erythrocytes were evaluated with a maximum deviation of 5%.
(3) The ratio was determined from at least the first 1000 erythrocytes counted.
(4) Significantly different from corresponding control group (Students *t* test, $p < 0.05$).

Table A.74(c)(ii) Combined micronucleus test and comet assay in rats: Overview Tail Intensity in liver cells (BPR Art. 95 dossier, 2015)

	Tail Intensity (%) [1]	S.D.
Vehicle Control	1.86	0.29
Sodium pyrithione 37.5 mg/kg	2.08	0.71
Sodium pyrithione 75 mg/kg	1.99	0.35
Sodium pyrithione 150 mg/kg	2.30	1.03
EMS 200 mg/kg	87.87*	4.48

[1] Five animals per treatment group; * = $p < 0.05$ (assessed with the Student's *t* test)
Vehicle Control = Elix water; EMS = Ethyl Methanesulfonate

Table A.74(c)(iii) Combined micronucleus test and comet assay in rats: Overview Tail Intensity in duodenum cells – 1st experiment (BPR Art. 95 dossier, 2015)

	Tail Intensity (%)[1]	S.D.
Vehicle Control	66.12	16.65
Sodium pyrithione 37.5 mg/kg	54.88	13.75
Sodium pyrithione 75 mg/kg	64.43	15.60
Sodium pyrithione 150 mg/kg	45.72	20.99
EMS 200 mg/kg	95.56*	2.52

[1] Five animals per treatment group; * = $p < 0.05$ (assessed with the Student's *t* test);
Vehicle Control = Elix water; EMS = Ethyl Methanesulfonate

Table A.74(c)(iv) Combined micronucleus test and comet assay in rats: Overview Tail Intensity in duodenum cells – 2nd experiment (BPR Art. 95 dossier, 2015)

	Tail Intensity (%)[1]	S.D.
Vehicle Control	47.29	9.26
Sodium pyrithione 37.5 mg/kg	55.73	11.24
Sodium pyrithione 75 mg/kg	60.27	18.08
Sodium pyrithione 150 mg/kg	70.96[a]	13.48
EMS 200 mg/kg	99.50*	0.12

[1] Five animals per treatment group; * = $p < 0.05$ (assessed with the Student's *t* test);
[a] = $p<0.05$ (assessed with the Dunnett's test); Vehicle Control = Elix water; EMS = Ethyl Methanesulfonate

Table A.74 Summary table of human data on genotoxicity
No human data is available.

A3.8.2.1 Short summary and overall relevance of the provided information on germ cell mutagenicity
Overall seven *in vitro* genotoxicity studies are available for sodium pyrithione: three Ames tests, one chromosome aberration test, two gene mutation tests and one UDS test.

In the three Ames tests (Doc IIIA A6.6.1/01, REACH registration dossier (2000), and BPR Art. 95 dossier (2014)), sodium pyrithione did not induce two-fold increases in the number of revertant colonies in the plate incorporation or pre-incubation assay, at any dose level, in any tester strain, in the absence and presence of S9 metabolism, indicating that sodium pyrithione is not mutagenic to *S. typhimurium* (TA 1535, TA 1537, TA 98, TA 100, TA 102) or *E. coli* (WP_2uvrA).

In a chromosomal aberration test in Chinese hamster V79 cells (Doc IIIA A6.6.2/01) sodium pyrithione was found to be positive. There was statistically significant increases in the number of cells bearing aberration (including and excluding gaps) in the absence and presence of S9 metabolism in the mid- and high-dose groups.

In a gene mutation test in Chinese hamster V79 cells (Doc IIIA A6.6.3/01), sodium pyrithione did not induce reproducible five-fold increases in mutant numbers or mutant frequency at any dose groups in the absence and presence of S9 metabolism.

Sodium pyrithione was negative also in another gene mutation test in Chinese hamster ovary cells (CHO/HRPT Mammalian Cell Forward Gene Mutation study) (Doc IIIA A6.6.3/02). Statistical analysis of the data indicated that there was no dose-dependent increases in the mutant frequencies in any of the treated groups in the absence and presence of S9 metabolism.

Sodium pyrithione was found to be negative also in the UDS test (Doc IIIA A6.6.7/01) under the condition that the highest dose group be excluded due to cytotoxicity; however the degree of cytotoxicity was not shown in detail.

The genotoxic potential of sodium pyrithione *in vivo* has been investigated in two micronucleus tests in mice and in a combined micronucleus test and comet assay in rats.

In the first micronucleus test in Crl:MMRI BR mice (Doc IIIA A6.6.4/01), no statistically significant increase in the amount of micronucleated polychromatic erythrocytes was observed at any doses tested compared to the negative controls, neither 24 nor 48 hours after treatment, neither for males nor for females. Bioavailability of the test substance was proven by mortality and by cytotoxicity at the high dose. This shows that sodium pyrithione does not produce relevant increases of the numbers of micronuclei in polychromatic erythrocytes after *in vivo* treatment of mice of either sex of the test strain at doses of 400, 482 and 580 mg/kg bw.

Also in the second micronucleus test in CD-1 mice (Doc IIIA A6.6.4/02), sodium pyrithione was negative at a dose level of 238 mg/kg bw administered in single intraperitoneal doses with sampling times of 30, 48, and 72 hours. These findings are based upon the inability of the test article to produce a significant increase in the incidence of micronuclei per 1000 polychromatic erythrocytes per animal in the treated groups versus the vehicle control group under the conditions of the test.

In the combined micronucleus test and comet assay in rats (BPR Art. 95 dossier, 2015), sodium pyrithione was negative in both tests

after oral gavage application for 3 consecutive days at dose levels 37.5, 75 and 150 mg/kg bw and a sampling time of 3-4 hours after the last dose. There was no statistically significant increase in amounts of micronucleated polychromatic erythrocytes compared to vehicle controls and no biologically relevant increase in the mean Tail Intensity (%) in liver and duodenum cells.

A3.8.2.2 Comparison with the CLP criteria
Annex I Section 3.5.1.1 of the CLP regulation defines mutation as a permanent change in the amount or structure of the genetic material in a cell. The term mutation applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications. The term 'mutagenic' and 'mutagen' are used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms. This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests *in vitro* and in mammalian somatic and germ cells *in vivo* are also considered in classifying substances within this hazard class.

Classification for mutagenicity in Category 1 is appropriate for substances known to induce heritable mutations (Category 1A) or for substances regarded as if they induce heritable mutations in the germ cells of humans (Category 1B).

Classification in Category 1A is based on positive evidence from human epidemiological studies.

Classification in Category 1B is based on positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with evidence that the substance has potential to cause mutations to germ cells; or positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny.
Classification for mutagenicity in Category 2 is appropriate for substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. Classification in Category 2 is based on positive evidence obtained from somatic cell mutagenicity tests in mammals and/or in some cases from somatic cell genotoxicity tests in mammals and supporting data from *in vitro* experiments.
All the available *in vitro* (except one) and *in vivo* studies with sodium pyrithione were negative. The negative micronucleus tests in mice shows the absence of a clastogenic potential in spite of the positive result in one *in vitro* chromosome aberration test. Therefore, sodium pyrithione is not genotoxic based on the available studies.

A3.8.2.3 Conclusion on classification and labelling for germ cell mutagenicity
Based on the available data, the DS proposes no classification for germ cell mutagenicity for sodium pyrithione according to the CLP criteria.

A3.8.2.4 Overall conclusion on genotoxicity related to risk assessment
Not applicable for the CLH report.

A.3.9. Carcinogenicity

Table A.75 Summary table of carcinogenicity studies in animals

Summary table of carcinogenicity studies in animals						
Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/ group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	NOAEL, LOAEL	Results (Please indicate any results that might suggest carcinogenic effects, as well as other toxic effects, for all dose levels)	Remarks (e.g. major deviations)	Reference
Combined chronic toxicity/carcinogenicity study, 104 weeks, Oral gavage, US EPA 83-2 (comparable to OECD 453), GLP: yes, Reliability: 2 (since information on purity and stability of the test substance was not investigated, and the survival was low in the test groups)	Rat Crl: CD (SD) (VAF Plus) 50/sex/dose	Sodium pyrithione (purity not specified; 41.41% aqueous solution was reported as purity by the applicant), Water, 0, 0.5, 1.5, 5 (decreased to 3.5 after 12 weeks) mg/kg bw/day	NOAEL < 0.5 mg/kg bw based on increased incidences of hind limb muscle wastage and spinal cord nerve fibres degeneration.	No evident sodium pyrithione-induced tumour increase. A minor incidence (in 2/20 males and 1/20 females) of hepatocellular carcinoma occurred in the top dose animals, without counterpart in controls in the chronic toxicity part of the study. The study report state that these tumours were within historical control limits. But according to the historical control data, there were between 1982-1990, for 104 week studies, up to 3/50 adenoma (6%) and up to 1/50 (2%) hepatocellular carcinoma in males and up to 5/50 (10%) adenomas in females and no incidence given for hepatocellular carcinoma. No hepatocellular carcinoma was reported in the carcinogenicity part of the study. But if the tumour incidences from both parts of the study are combined this gives a frequency of 2/70 (2.9%) in males and 1/70 (1.4%) in females. Hepatocellular adenomas occurred in 3/50 males and 1/50 females of the maximum dose tested and 1/50 females at 1.5 mg/kg bw/day, in the carcinogenicity part of the study. The information given on the historical control data were limited, the only information given were that the data were from studies performed during 1982-1990 (n=10) on untreated CD (SD) BR rats for 104 weeks.	-	Doc IIIA A6.5.1/01 and A6.7/01 Year: 1991 (unpublished)
Combined chronic toxicity/carcinogenicity study, 104 weeks, Oral gavage, EPA OPPTS	Rat Hsd: Sprague Dawley SD Control, low and medium	Sodium pyrithione (purity not specified; 40.8% aqueous solution was reported as purity by the applicant), Distilled water, 0, 0.5, 1.4, 4 (decreased	NOAEL < 0.5 based on sciatic nerve degeneration in 1/12 males	No evident sodium pyrithione-induced tumour increase. Peripheral nervous tissue (the sciatic nerve was investigated histopathologically) and skeletal muscle are the main targets of toxic action and related clinical signs such as ataxia, necropsy findings and histological changes were found in the 3 dosed groups in both sexes in a dose-related expression.	-	Doc IIIA A6.5.1/02 and A6.7/02 Year: 2004 (unpublish

870.4300 (comparable to OECD 453), GLP: yes, Reliability: 2 (since the survival rate was low)	dose: 12/sex/dose; high dose: 20/sex/dose.	to 2.8 after 7 weeks and decreased to 2.1 for female after 9 months) mg/kg bw/day Duration of exposure: at least 104 weeks, with the exception of low dose group males, which were sacrificed during week 98		Changes in relative organ to body weights occurred in several organs in females at the highest dose tested (kidneys, heart, ovaries, liver, adrenals, brain). Vascular mineralization of lungs and alveolar haemorrhage was observed histopathologically in males at the highest doses (but not statistically significant).		ed)
Carcinogenicity study, 80 weeks, Dermal, US EPA 83-2 (comparable to OECD 451), GLP: yes, Reliability: 1	Mouse Crl: CD-1 (ICR) BR (VAF plus) 50/sex/dose	Sodium pyrithione (purity not specified; 41.2% aqueous solution was reported as purity by the applicant), Distilled water, 0, 5, 15, 40 mg/kg bw/day	NOAEL: 5 mg/kg bw LOAEL: 15 mg/kg bw based on increased incidence of epidermal hyperplasia	No evident sodium pyrithione-induced tumour increase. No increase in hepatocellular carcinoma was observed (one animal in the lowest dose group had a hepatocellular carcinoma). Instead a biliary carcinoma was observed in the highest dose.	-	Doc IIIA A6.7.1/03 Year: 1991 (unpublished)

Table A.76(a) Results of the oral rat combined chronic toxicity/carcinogenicity study (**Doc IIIA A6.5.1/01 and A6.7/01**)

	control data				**0. 5 mg/Kg low dose**		**1.5 mg/Kg medium dose**		**5.0 mg/Kg [1] high dose**		**dose-response + / -**	
	historical		**study**									
Parameter	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
	If differing numbers of animals are examined, give number affected/number of animals examined for each individual finding.											
Number of animals examined	500	500	50	50	50	50	50	50	50	50		
Mortality			32	21	33	25	33	26	26	25	-	-
clinical signs:												
hind-limb muscle wastage			1	1	2	3	1	2	10	16	+	+
body weight gain			ne	ne	ne	ne	ne	↓	ne	↓	-	+
food consumption			ne	ne	ne	ne	ne	ne	ne	ne	-	-
Overall tumour incidence:												
No. of animals with neoplasms	444	455	39	45	33	43	35	44	42	44	-	-

Parameter	control data				0. 5 mg/Kg low dose		1.5 mg/Kg medium dose		5.0 mg/Kg [1] high dose		dose-response + / -	
	historical		study									
	m	f	m	f	m	f	m	f	m	f	m	f
No. of animals with benign neoplasms			61	74	40	59	39	68	66	64	-	-
No. of animals with malignant neoplasms			10	6	12	10	6	12	12	12	-	-
No. of animals with > 1 neoplasm	266	307	— [2]	—	—	—	—	—	—	—		
Spinal cord:												
Nerve fiber degeneration			28/50	23/50	16/33	6/25	7/33	5/26	35/50	28/50	+	+
Sciatic nerve:												
Nerve fiber degeneration			15/50	12/50	6/33	4/25	6/33	4/26	30/50	26/50	+	+
Skeletal muscle:												
Degeneration			10/50	1/50	9/50	5/50	13/50	8/50	34/50	38/50	+	+
Eyes:												
Retinal atrophy			8/50	8/50	2/34	3/25	4/33	8/27	13/50	34/50	-	+

[1] The 5 mg/Kg dose was reduced to 3.5 mg/Kg after 12 weeks.
[2] Results not reported in this format.
ne: no effect.

Table A.76(b) Results of the oral rat combined chronic toxicity/carcinogenicity study (**Doc IIIA A6.5.1/02 and A6.7/02**)

Parameter	control		low dose		medium dose		high dose	
	m	f	m	f	m	f	m	f
Number of animals examined	56	56	56	56	56	56	56	56
Mortality	37	25	40	25	40	34	41	37
No. of primary tumours	61	84	25	88	50	77	45	63
No. of animals with neoplasms	40	51	16	49	38	48	27	41
No. of animals with > 1 neoplasm	16	27	6	30	11	24	13	15
Overall tumour incidence	61	84	25	88	50	77	45	63
No. of animals	55	78	21	80	43	69	36	55

Parameter	control		low dose		medium dose		high dose	
	m	f	m	f	m	f	m	f
with benign neoplasms								
No. of animals with malignant neoplasms	6	6	4	8	7	8	9	8

Table A.76(c) Results of the dermal mice carcinogenicity study (**Doc IIIA A6.7.1/03**)

	control data				5 mg/Kg low dose		15 mg/Kg medium dose		40 mg/Kg high dose		dose-response + / -	
	historical		study									
Parameter	m	f	m	f	m	f	m	f	m	f	m	f
Number of animals examined	200	200	50	50	50	50	50	50	50	50		
Mortality			9	14	6	14	5	8	8	13	-	-
clinical signs			ne	ne	ne	ne	ne	ne	ne	ne	-	-
body weight gain			ne	ne	ne	ne	ne	ne	ne	ne	-	-
food consumption			ne	ne	ne	ne	ne	ne	ne	ne	-	-
haematology			ne	ne	ne	ne	ne	ne	ne	ne	-	-
Overall tumour incidence:												
No. of animals with neoplasms			21	29	21	20	22	13	25	22	-	-
No. of animals with benign neoplasms			16	7	12	11	15	4	12	9	-	-
No. of animals with malignant neoplasms			5	22	9	9	7	9	13	13	-	-
Total number of tumour bearers	52%	39%	35%	48%	36%	36%	38%	22%	40%	42%	-	-

ne: no effect

Table A.76 Summary table of human carcinogenicity data
No human data is available.

Table A.77 Summary table of other relevant studies for carcinogenicity
No other data is available.

A3.9.1 Short summary and overall relevance of the provided information on carcinogenicity
Two 2-year oral combined toxicity/carcinogenic studies in rats and one 80 weeks dermal carcinogenicity study in mice performed with NaPT are available for the evaluation of carcinogenicity.

In the first 2-year oral combined toxicity/carcinogenicity study (Doc IIIA A6.5.1/01 and A6.7/01), rats were exposed to 0.5, 1.5 and 5 (decreased to 3.5 after 12 weeks) mg-NaPT/kg bw/day. In the second 2-year oral combined toxicity/carcinogenicity study (Doc IIIA A6.5.1/02 and A6.7/02), rats were exposed to 0.5, 1.4, 4 (decreased to 2.8 after 7 weeks and decreased to 2.1 for females after 9 months) mg-NaPT/kg bw/day. In the dermal 80 weeks carcinogenicity study (Doc IIIA A6.7.1/03), mice were exposed 5, 15, 40 mg-NaPT/kg bw/day.

Neither of the studies with oral exposure of NaPT to rats meets the criteria for a truly negative carcinogenicity study since survival was less than 50 % in some groups. However, there is no indication of increased tumour formation due to NaPT exposure in neither the two oral studies in rats nor in the dermal study in mice.

Table A.78 Compilation of some factors that may be taken into consideration in classification and labelling
No evident sodium pyrithione-induced tumour increase in the available studies.
A.3.9.2 Comparison with the CLP criteria
Annex I Section 3.6.1.1 of the CLP Regulation defines a carcinogen as a substance which induces cancer or increase its incidence. Substances which have induced benign and malignant tumours in well-performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans. Carcinogenic substances are allocated to Category 1 (known or presumed human carcinogens) or Category 2 (suspected human carcinogens).

A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. Substances known to have carcinogenic potential in humans (based largely on human evidence) are classified in Category 1A. Substances presumed to have carcinogenic potential for humans (based largely on animal evidence) are classified in Category 1B. A substance is classified in Category 2 for carcinogenicity on the basis of human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B.

There is no evidence for carcinogenicity for sodium pyrithione from the two oral rat and one dermal mice carcinogenicity studies.

A.3.9.3 Conclusion on classification and labelling for carcinogenicity
Based on the available data, the DS proposes no classification for carcinogenicity for sodium pyrithione according to the CLP criteria.

A.3.9.4 Overall conclusion on carcinogenicity related to risk assessment
Not applicable for the CLH report.

A.3.10. Reproductive toxicity

A.3.10.1. Sexual function and fertility

Table A.79 Summary table of animal studies on adverse effects on sexual function and fertility

Summary table of animal studies on adverse effects on sexual function and fertility						
Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/ group	Test substance (including purity), Vehicle, Dose levels Duration of exposure	NOAELs, LOAELs (e.g. maternal/parental toxicity, effects on sexual function and fertility)	Results (for all dose levels, specify critical effects on sexual function and fertility for parental animals (and offspring if relevant), report e.g. incidences and severity of the effects for all dose levels)	Remarks (e.g. major deviations)	Reference
2-generation reproduction toxicity study, Oral gavage, US EPA 83-4, GLP: Yes, Reliability: 1, Key study	Rat Crl:CD(SD)BR 25/sex/group	Sodium pyrithione (purity not specified; 41.2% aqueous solution), Water, 0, 0.5, 1.5, and 3.5 (4.5 during first three weeks) mg/kg bw, Starting 11 weeks before mating until sacrifice	NOAEL - parental: 0.5 mg/kg bw/day. LOAEL – parental: 1.5 mg/kg bw/day (atrophy of hind limb muscles in F1 females). NOAEL – reproduction: 1.5 mg/kg bw/day. LOAEL – reproduction: 3.5 mg/kg bw/day (reductions in the number of animals mating and number fertile. Increase in the time taken to mate in P animals)	<u>P animals – 3.5 mg/kg bw/day:</u> ↓ body weight (♀ and ♂) compared to control from week 3 throughout most of the study, including during gestation and lactation (ca -4-9%, p<0.01) ↑ atrophy of skeletal muscle fibres from the upper hind limb with related hind limb paralysis/impairment of movement (♂:8; ♀: 19) ↓ number of animals mating (70.8 % of number paired, p<0.05) ↓ percentage of matings resulting in pregnancy (70.6 % of number mated, p<0.05) ↑ time taken to mate, not statistically significant <u>F1 adults – 3.5 mg/kg bw/day:</u> ↑ mortality, 2 ♀ killed *in extremis* ↓ body weight gain, (♀: -9-11 %, p<0.0001, throughout gestation and lactation; ♂: -5%, p<0.05 but not statistically significant when compared individually ↓ food consumption at the pre-mating period (♀: -8%, p<0.01) ↑ atrophy of skeletal muscle fibres from the upper hind limb with related hind limb paralysis/impairment of movement (9 ♂ and 20 ♀) <u>F1 adults – 1.5 mg/kg bw/day:</u> ↑ atrophy of skeletal muscle fibres from the upper hind limb with related hind limb paralysis/impairment of movement (3	Study is equivalent to OECD 416 with the following deviations: the oestrus cycle was not monitored in parental animals during the three weeks before the mating period; No sperm characterization ; No organ weights; Number of implantations, corpora lutea and post implantation loss was not determined; Testes were fixed in 10% formalin solution. Spinal	Doc IIIA A6.8.2/01 Year: 1989 (unpublished)

				♀)	cord and sciatic nerve were not subjected to histopathology.	
2-generation reproduction toxicity study, Oral gavage, US EPA OPPTS 870.3800, GLP: Yes, Reliability: 1, Key study	Rat Hsd: Sprague Dawley 24/sex/ group (plus 8 additional animals per sex in the high dose group)	Sodium pyrithione (purity not specified; 40.8% aqueous solution), Water, 0, 0.7, 1.4, 2.8 mg/kg bw, Starting 10 weeks before mating until sacrifice	NOAEL - parental: 0.7 mg/kg bw/day. LOAEL – parental: 1.4 mg/kg bw/day (based on the significantly decreased kidney weights in P females. Since no histopathology was performed on kidney, the decrease is considered as adverse). NOAEL – reproduction: 2.8 mg/kg bw/day (highest dose tested).	<u>P animals – 2.8 mg/kg bw</u>: ↑ emaciation during weeks 1-17 (16 ♀) ↓ food consumption (♂: -6%, p<0.01; ♀: -8%, p<0.05, on gestation day 7-11-19%, p<0.01, post-partum days 14 and 21) ↓ body weights (♂: -5%, p<0.01, ♀: -9%, p<0.01, during pre-mating, gestation and post-partum periods from day 22) ↓ terminal body weights (♂+♀: -12%, p<0.01) <u>P animals – all dose groups</u>: ↓ fertility index (♂+♀): 87.5% in low-dose, 79.2% in mid-dose and 83.9% in high-dose <u>F1 adults – 2.8 mg/kg bw</u>: ↑ number of days taken for preputial separation (mean 45.38 compared to mean 44.17 in control, p<0.05) ↑ emaciation during nominal weeks 5-17 (5 ♀), ↓ body weights (-8-11% in ♂ on nominal days 28-42 (p<0.01), and -6% in ♀ (p<0.01) on nominal days 77-91) ↓ food consumption on nominal days 35 and 42, gestation days 7 and 14 and post-partum day 21 (- 6-12% in ♀, p<0.01)	Deviations: Thyroid weight was not reported; Only 10 random selected P and F1 adults were selected for histopathology while according to the guideline it should be for all animals of the high dose and control group. Furthermore, the previously identified target organs skeletal muscle, sciatic nerve and spinal cord were not investigated.	Doc IIIA A6.8.2/02 Year: 2003 (unpublished)

Table A.80(a)(i) Details of the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/01**)

Parameter			**Control**		**low dose**		**medium dose**		**high dose**	
		Genera-tion	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
Mortality	Incidence	**P**	0	0	0	0	0	0	0	1*
		F_1	0	0	0	0	0	0	0	2*
		F_2	0	0	0	0	0	0	0	0

		*Humanely killed because of poor clinical condition following the observation of hind limb paralysis or impairment of hind limb movement								
Food consumption	effect	**P**	-	-	↑**	↑*	↑*	ne	↓*	↓**
		F_1	-	-	↑*	ne	↑**	ne	ne	↓**
Body weight gain	effect	**P**	-	-	ne	ne	↑*	ne	↓**	↓**
		F_1	-	-	↑*	ne	↑*	ne	↓***	ne
		*significantly different from control (≥1 week), p<0.05 **significantly different from control (≥1 week), p<0.01 ***significantly different from control (≥1 week), p<0.001								
Clinical Observations	Incidence									
hunched posture, fur staining on ventral abdomen, impaired hind limb mobility, rapid breathing, peri-orbital and peri-nasal staining		**P**	ne	ne	ne	ne	ne	ne	ne	1
hunched posture, hind limb paralysis, emaciation, slight ataxia, increased respiration arte		**F_1**	ne	ne	ne	ne	ne	ne	ne	2
Organ weights	Not taken									
Macroscopic pathology	*Incidence*									
Hind limb muscle wastage		**P**	ne	ne	ne	ne	ne	ne	ne	1
		F_1	ne	ne	ne	ne	ne	ne	ne	2
Red fluid in ileum, mix of food and saw dust in stomach		**P**	ne	ne	ne	ne	ne	ne	ne	ne
		F_1	ne	ne	ne	ne	ne	ne	ne	1
Histopathologic examination	Incidence									
Atrophy of the skeletal muscle from the upper hind limb, characterized by reduction and variation in the		**P**	ne	ne	ne	ne	ne	ne	8	19

diameter of muscle fibers, and apparent increase in the number of sarcolemmal nuclei and fatty replacement of muscle fibers.		**F_1**	ne	ne	ne	ne	ne	3	9	20
Reproductive Performance										
Mating index		**P**	95.7	96.0	96.0	96.0	84.0	92.0	70.8	87.5
		F_1	76.0	100	60.0	84.0	72.0	96.0	58.3	95.7
Fertility index		**P**	95.5	95.8	91.7	91.7	95.2	95.7	70.6	76.2
		F_1	94.7	92.0	80.0	85.7	72.2	79.2	92.9	90.9
Number of implantation sites	Not determined									
Duration of pregnancy	Mean	**P**	-	21.9	-	22.1	-	22.2	-	22.1
		F_1	-	22.4	-	22.2	-	22.3	-	22.3
Birth index										
Live birth index		**P**	-	96.5	-	99.0	-	97.2	-	96.2
		F_1	-	93.7	-	97.9	-	93.4	-	97.2
Gestation index		**P**	-	100	-	100	-	100	-	100
		F_1	-	100	-	100	-	100	-	100
Litter size	Mean	**P**	-	11.4	-	12.5	-	11.2	-	10.4
		F_1	-	11.2	-	11.7	-	11.3	-	10.0
Litter weight	Not reported. Refer to day-0 means below.									
Pup weight	Mean									

Day 0		**P**	5.9	5.6	6.1	5.8	6.2	5.9	6.3	5.8
Day 4			9.1	8.7	9.4	9.0	9.5	9.1	9.0	8.4
Day 7			14.7	14.2	15.2	14.8	14.9	14.2	14.9	13.6
Day 14			30.9	30.0	32.2	31.1	30.0	28.7	29.6	28.3
Day 21			49.1	47.4	51.8	49.8	48.4	46.3	47.9	44.8
Day 0		**F_1**	5.9	5.6	6.0	5.6	6.2	5.6	6.1	5.8
Day 4			8.63	8.1	8.8	8.2	8.6	8.2	9.1	8.6
Day 7			14.1	13.4	14.7	13.7	13.7	13.3	13.9	13.3
Day 14			29.8	29.1	30.5	29.3	28.2	27.4	28.0	26.6
Day 21			47.3	46.4	48.6	45.3	46.0	44.0	45.2	42.1
Sex ratio	Male/female	**P**	49	51	48	52	54	46	58	42
		F_1	53	47	53	47	50	50	48	52
Survival index		**P**	-	85.9	-	86.0	-	94.1	-	87.4
		F_1	-	66.5	-	80.4	-	74.3	-	81.0
Viability index		**P**	-	89.5	-	87.7	-	97.3	-	97.3
		F_1	-	68.0	-	84.1	-	81.6	-	82.6
Lactation index		**P**	**-**	95.1	-	98.9	-	99.4	-	93.8
		F_1	-	98.7	-	94.1	-	94.1	-	99.3
Sperm characterization	*Not part of the study guideline*									
Number	% of control									

Deformations	% of control									

ne - no biologically or statistically significant effects

Table A.80(a)(ii) Group mean body weight (in grams) ± S.D of P males in the 2-generation reproductive toxicity study (**Doc IIIA A6.8.2/01**)

Weeks	Dose level (mg/kg/day)				Analysis of variance
	Control	0.5	1.5	3.5	
1	242 ± 9	242 ± 9	242 ± 9	242 ± 9	NS
2	279 ± 12	280 ± 13	285 ± 11	281 ± 14	NS
3	328 ± 12	324 ± 17	331 ± 17	318 ± 17*	p < 0.05
4	364 ± 13	359 ± 22	368 ± 18	351 ± 23*	p < 0.05
5	379 ± 15	380 ± 29	393 ± 21*	364 ± 28*	p < 0.001
6	413 ± 22	405 ± 32	418 ± 27	390 ± 33**	p < 0.01
7	437 ± 23	430 ± 35	442 ± 30	411 ± 35**	p < 0.01
8	447 ± 24	443 ± 38	453 ± 31	422 ± 39**	p < 0.01
9	469 ± 26	461 ± 41	475 ± 36	443 ± 45*	p < 0.05
10	487 ± 27	477 ± 42	490 ± 38	453 ± 41**	p < 0.01
11	495 ± 30	488 ± 44	503 ± 41	462 ± 42**	p < 0.01
12	510 ± 32	503 ± 46	517 ± 39	474 ± 46**	p < 0.01
13	518 ± 34	510 ± 48	527 ± 44	486 ± 46**	p < 0.01
14	528 ± 36	523 ± 53	538 ± 46	488 ± 49**	p < 0.01
15	536 ± 39	531 ± 53	542 ± 45	490 ± 51**	p < 0.001
16	544 ± 41	540 ± 54	551 ± 48	499 ± 52**	p < 0.01

* = significantly different from control, p < 0.05, Student's t test.
** = significantly different from control, p < 0.01, Student's t test.

Table A.80(a)(iii) Group mean body weight (in grams) ± S.D of P females in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/01**)

Week pre-mating	Control	Dose level (mg/kg/day) 0.5	1.5	3.5	Analysis of variance
1	183 ± 7	183 ± 6	183 ± 7	183 ± 6	NS
2	196 ± 8	198 ± 8	197 ± 8	198 ± 10	NS
3	208 ± 11	211 ± 10	210 ± 11	200 ± 14*	$p < 0.01$
4	220 ± 11	221 ± 11	221 ± 12	202 ± 19***	$p < 0.001$
5	229 ± 13	232 ± 15	230 ± 14	207 ± 21***	$p < 0.001$
6	237 ± 14	243 ± 16	241 ± 16	219 ± 20***	$p < 0.001$
7	244 ± 14	249 ± 15	249 ± 18	232 ± 20*	$p < 0.01$
8	253 ± 17	257 ± 18	256 ± 18	241 ± 21*	$p < 0.05$
9	255 ± 17	259 ± 19	260 ± 20	244 ± 21*	$p < 0.05$
10	262 ± 18	266 ± 19	267 ± 22	253 ± 22	NS
11	263 ± 18	269 ± 20	269 ± 22	256 ± 23	NS
12	267 ± 21	276 ± 22	276 ± 24	259 ± 24	$p < 0.05$
Day of pregnancy					
0	266 ± 17	276 ± 19	275 ± 23	251 ± 16	$p < 0.01$
7	282 ± 19	294 ± 20	288 ± 26	260 ± 18**	$p < 0.001$
14	307 ± 19	318 ± 21	309 ± 26	279 ± 15***	$p < 0.001$
20	365 ± 22	379 ± 25	362 ± 30	332 ± 21***	$p < 0.001$
Day post partum					
0	287 ± 22	293 ± 29	293 ± 23	269 ± 20*	$p < 0.05$
7	300 ± 17	311 ± 23	301 ± 22	279 ± 15**	$p < 0.001$
14	311 ± 18	320 ± 22	308 ± 20	285 ± 17***	$p < 0.001$
21	300 ± 19	311 ± 24	302 ± 18	290 ± 16	$p < 0.05$

* = significantly different from control, $p < 0.05$, Student's t test.
** = significantly different from control, $p < 0.01$, Student's t test.
*** = significantly different from control, $p < 0.001$, Student's t test.

Table A.80(a)(iv) Group mean body weight (in grams) ± S.D of F1 males in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/01**)

Approximate age (weeks)	Dose level (mg/kg/day)				Analysis of variance
	Control	0.5	1.5	3.5	
4	53 ± 5	54 ± 5	52 ± 7	50 ± 5	NS
5	91 ± 9	93 ± 10	92 ± 11	90 ± 9	NS
6	142 ± 12	144 ± 16	145 ± 16	141 ± 12	NS
7	214 ± 23	216 ± 27	214 ± 22	212 ± 26	NS
8	265 ± 27	269 ± 33	268 ± 27	264 ± 27	NS
9	317 ± 27	319 ± 37	319 ± 30	313 ± 29	NS
10	350 ± 28	355 ± 41	355 ± 32	346 ± 29	NS
11	379 ± 31	385 ± 46	387 ± 33	374 ± 31	NS
12	405 ± 36	413 ± 49	413 ± 36	400 ± 33	NS
13	424 ± 36	429 ± 51	431 ± 35	418 ± 39	NS
14	437 ± 37	451 ± 52	453 ± 39	434 ± 37	NS
15	455 ± 37	472 ± 53	475 ± 41	449 ± 37	NS
16	472 ± 39	488 ± 58	493 ± 42	467 ± 43	NS
17	487 ± 38	503 ± 58	504 ± 43	474 ± 46	NS
18	490 ± 39	506 ± 57	511 ± 44	479 ± 45	NS
19	503 ± 41	520 ± 61	521 ± 48	482 ± 46	$p < 0.05$
20	517 ± 44	530 ± 64	533 ± 52	490 ± 51	$p < 0.05$
21	526 ± 45	539 ± 69	545 ± 53	500 ± 53	$p < 0.05$
22	537 ± 49	549 ± 79	557 ± 54	510 ± 54	$p < 0.05$
23	550 ± 47	565 ± 76	568 ± 57	519 ± 51	$p < 0.05$

Table A.80(a)(v) Group mean body weight (in grams) ± S.D of F1 females in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/01**)

Approximate age (weeks)	Dose level (mg/kg/day) Control	0.5	1.5	3.5	Analysis of variance
4	50 ± 6	52 ± 6	48 ± 5	46 ± 5**	p < 0.001
5	85 ± 9	87 ± 8	83 ± 9	80 ± 7*	p < 0.05
6	124 ± 13	127 ± 11	123 ± 11	119 ± 9	NS
7	163 ± 15	162 ± 14	160 ± 17	157 ± 13	NS
8	186 ± 17	185 ± 16	186 ± 20	184 ± 14	NS
9	208 ± 18	205 ± 18	204 ± 25	202 ± 15	NS
10	222 ± 20	219 ± 19	222 ± 27	217 ± 15	NS
11	233 ± 21	233 ± 20	235 ± 26	225 ± 17	NS
12	244 ± 22	244 ± 20	247 ± 31	234 ± 18	NS
13	252 ± 25	251 ± 20	256 ± 34	241 ± 17	NS
14	261 ± 24	260 ± 20	265 ± 34	247 ± 19*	NS
15	262 ± 23	260 ± 21	271 ± 37	249 ± 20*	NS
16	271 ± 24	269 ± 23	277 ± 39	252 ± 23*	p < 0.05
17	277 ± 26	276 ± 21	286 ± 42	255 ± 23*	p < 0.05
Day of pregnancy					
0	276 ± 27	270 ± 18	275 ± 22	252 ± 24**	p < 0.05
7	295 ± 28	290 ± 21	293 ± 27	264 ± 26***	p < 0.001
14	318 ± 29	312 ± 21	317 ± 28	281 ± 24***	p < 0.001
20	369 ± 31	372 ± 27	371 ± 40	330 ± 26***	p < 0.001
Day post partum					
0	296 ± 27	297 ± 27	301 ± 30	272 ± 28**	p < 0.01
7	311 ± 23	312 ± 23	305 ± 26	280 ± 24***	p < 0.001
14	320 ± 23	327 ± 24	318 ± 27	293 ± 22***	p < 0.001
21	308 ± 24	313 ± 22	304 ± 29	290 ± 20*	p < 0.05

* = significantly different from control, p < 0.05, Student's t test.
** = significantly different from control, p < 0.01, Student's t test.
*** = significantly different from control, p < 0.001, Student's t test.

Table A.80(a)(vi) Group mean pup body weight (in grams) ± S.D of F1 generation in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/01**)

Dose level (mg/kg/day)	Sex	Day post partum 0	4	7	14	21
Control	M	5.9 ± 0.6	9.1 ± 1.4	14.7 ± 1.9	30.9 ± 2.8	49.1 ± 4.3
0.5	M	6.1 ± 0.6	9.4 ± 1.6	15.2 ± 2.3	32.2 ± 3.1	51.8 ± 4.8
1.5	M	6.2 ± 0.5	9.5 ± 1.6	14.9 ± 2.2	30.0 ± 3.7	48.4 ± 5.6
3.5	M	6.3 ± 0.6	9.0 ± 1.2	14.9 ± 1.4	29.6 ± 3.5	47.9 ± 4.6
Analysis of variance		NS	NS	NS	NS	NS
Control	F	5.6 ± 0.5	8.7 ± 1.7	14.2 ± 2.0	30.0 ± 2.7	47.4 ± 4.0
0.5	F	5.8 ± 0.5	9.0 ± 1.6	14.8 ± 2.3	31.1 ± 3.5	49.8 ± 5.0
1.5	F	5.9 ± 0.5	9.1 ± 1.6	14.2 ± 2.2	28.7 ± 3.4	46.3 ± 5.3
3.5	F	5.8 ± 0.5	8.4 ± 1.2	13.6 ± 2.0	28.3 ± 3.2	44.8 ± 5.0
Analysis of variance		NS	NS	NS	$p < 0.05$	$p < 0.05$

Table A.80(a)(vii) Group mean pup body weight (in grams) ± S.D of F2 generation in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/01**)

Dose level (mg/kg/day)	Sex	Day post partum 0	4	7	14	21
Control	M	5.9 ± 0.6	8.6 ± 1.3	14.1 ± 2.2	29.8 ± 3.4	47.3 ± 5.5
0.5	M	6.0 ± 0.6	8.8 ± 2.0	14.7 ± 2.2	30.5 ± 3.4	48.6 ± 5.9
1.5	M	6.2 ± 0.6	8.6 ± 1.1	13.7 ± 2.3	28.2 ± 2.6	46.0 ± 4.8
3.5	M	6.1 ± 0.5	9.1 ± 1.3	13.9 ± 2.4	28.0 ± 3.8	45.2 ± 6.4
Analysis of variance		NS	NS	NS	NS	NS
Control	F	5.6 ± 0.5	8.1 ± 1.2	13.4 ± 1.8	29.1 ± 2.9	46.4 ± 4.6
0.5	F	5.6 ± 0.7	8.2 ± 1.9	13.7 ± 2.5	29.3 ± 5.4	45.3 ± 6.4
1.5	F	5.6 ± 0.4	8.2 ± 1.2	13.3 ± 2.0	27.4 ± 2.4	44.0 ± 4.5
3.5	F	5.8 ± 0.6	8.6 ± 1.2	13.3 ± 1.7	26.6 ± 2.8	42.1 ± 5.1
Analysis of variance		NS	NS	NS	NS	NS

Table A.80(b)(i) Details of the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Parameter		**generation**	**control**		**low dose**		**medium dose**		**high dose**	
			m	**f**	**m**	**f**	**m**	**f**	**m**	**f**
Mortality	incidence	**P**	nr	0	nr	0	nr	1	nr	0
Humane kill	incidence	**P**	nr	1	nr	0	nr	0	nr	1
Food consumption		**P**	-	-	-	-	-	-	↓	↓
		F1	nf	-	nf	-	nf	-	nf	↓
Body weight gain		**P**							↓	↓
		F1							↓	↓

Parameter		generation	control		low dose		medium dose		high dose	
			m	f	m	f	m	f	m	f
Clinical Observations emaciation emaciation		**P** **F1**	0 0	1 0	0 0	0 0	 0	0 0	0 0	16 5
Organ weights kidneys uterus kidneys uterus spleen epididymides		**P** **F1**	 nf - nf nf nf nf	 - - nf nf nf	 nf - nf nf nf	 - - nf nf nf	 nf - nf nf nf	 ↓ ↑ nf nf nf	 nf - nf nf ↓	 ↓ ↑ nf nf ↑
Pathology		**P** **F1**	nf nf	nf nf	nf nf	nf nf	nf nf	nf nf	nf nf	nf nf
Histopathologic examination		**P** **F1**	nf nf	nf nf	nf nf	nf nf	nf nf	nf nf	nf nf	nf nf
Not pregnant		**P** **F1**	 	0 4	 	3 8	 	5 0	 	5 2
Mating not detected		**F1**		1		0		0		0
Unilateral implantation		**P** **F1**	 	1 0	 	0 1	 	0 0	 	0 1
Total resorption		**F1**		0		1		0		2
Total litter loss		**P** **F1**	 	3 0	 	0 0	 	0 0	 	0 1

Parameter		generation	control		low dose		medium dose		high dose	
			m	f	m	f	m	f	m	f
Premature birth		P		0		0		1		0
With live pups on Day 21 post-partum		P		21		21		18		26
		F1		20		15		24		27
Mating index	%	P	100	100	100	100	100	100	96.8	100
		F1	88	100	96	100	96	100	100	100
Fertility index	%	P	100	100	87.5	87.5	79.2	79.2	83.9	83.9
		F1	95	83	65	61	100	100	94	94
Number of implantation sites	Mean	P		14.1		15.0		14.8		13.3
		F1		14.5		12.9		14.2		15.0
Duration of pregnancy	Mean	P		22		22		22		22
		F1		22		22		22		22
Pre-birth loss	Mean	P		1.0		1.9		2.1		1.7
		F1		1.1		0.67		1.42		1.25
Litter size at birth	Mean	P		13.5		13.1		12.7		11.6
		F1		13.4		12.3		12.8		13.7
Litter size, live, at birth	Mean	P		12.2		11.9		11.2		10.7
		F1		12.8		11.3		11.8		12.9
Litter weight, at birth	Mean, g	P		76.7		75.9		73.0		68.9

Parameter		generation	control		low dose		medium dose		high dose	
			m	f	m	f	m	f	m	f
		F1		78.9		70.6		74.3		80.6
Pup weight, at birth	Mean, g	P		6.3		6.4		6.5		6.4
		F1		6.2		6.3		6.4		6.3
Sex ratio, at birth	% males	P		52.3		48.0		52.0		50.5
		F1		45.1		44.3		46.7		52.4
Litter size, live, at Day4	Mean	P		11.5		11.6		10.9		10.1
		F1		12.4		11.1		10.8		13.1
Lactation index	%	P		98.8		97.0		96.5		99.5
		F1		98.7		100.0		96.8		99.5
Mean pup weight, at Day 21	Mean, g	P		48.6		45.9		43.1		40.1
		F1		46.7		47.0		43.7		35.8
Sperm characterization		P	nf		nf		nf		nf	
		F1	nf		nf		nf		nf	

nr: not reported
nf: no treatment related findings

Table A.80(b)(ii) Body weight (in grams) of P males in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group(s)		Day of Phase 1!	1"	8	15	22	29	36	43	50
1	(n)	24	24	24	24	24	24	24	24	24
	Mean	204.83	250.75	287.93	317.55	341.93	364.01	379.80	392.91	405.86
	SD	10.00	11.94	14.80	16.51	19.24	20.84	22.71	23.08	25.17
2	(n)	24	24	24	24	24	24	24	24	24
	Mean	204.57	251.79	289.47	322.14	347.34	370.09	386.25	400.92	411.31
	SD	9.20	9.07	10.26	12.35	14.01	16.23	17.91	19.95	21.73
3	(n)	24	24	24	24	24	24	24	24	24
	Mean	204.51	248.69	285.44	318.24	344.06	366.36	382.29	393.53	405.46
	SD	8.55	9.73	12.46	14.35	14.68	17.12	18.46	17.64	19.03
4	(n)	32	32	32	32	32	32	32	32	32
	Mean	204.70	249.91	281.87	310.50	333.55	351.98*	367.71	380.03	390.64*
	SD	8.99	10.66	12.17	15.04	18.24	19.38	21.20	21.34	22.39

Group(s)		Day of Phase 57	64	71	78	85	92	99	106	113	120
1	(n)	24	24	24	24	24	24	24	24	24	24
	Mean	417.05	427.61	435.57	435.58	445.91	450.77	457.91	464.61	468.44	468.43
	SD	24.64	26.51	26.53	27.83	27.26	29.43	28.55	28.70	28.90	29.15
2	(n)	24	24	24	24	24	24	24	24	24	24
	Mean	424.67	435.50	440.58	442.22	450.46	454.26	466.06	470.29	476.13	478.48
	SD	23.40	24.70	24.68	25.78	25.95	27.59	28.52	28.89	29.01	29.38
3	(n)	24	24	24	24	24	24	24	24	24	24
	Mean	418.87	428.88	434.91	436.13	445.77	451.67	459.07	464.67	469.62	473.05
	SD	19.53	20.71	21.88	21.63	21.62	21.64	23.75	21.22	22.64	22.34
4	(n)	32	32	32	32	32	32	32	32	32	32
	Mean	401.59*	412.26	416.00**	414.14**	421.80**	430.18*	433.84**	438.57**	440.59**	442.24**
	SD	23.23	23.47	22.48	23.36	23.26	24.86	25.58	25.07	25.62	25.95

Note: Data for Dosing phase
 * = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are nonhomogeneous ($)

Table A.80(b)(iii) Body weight (in grams) of P females before pairing in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

		Day of Phase											
Group(s)		1!	1"	8	15	22	29	36	43	50	57	64	71
1	(n)	24	24	24	24	24	24	24	24	24	24	24	24
	Mean	166.52	187.63	200.77	214.51	228.32	236.31	243.89	249.57	255.21	261.36	269.16	269.90
	SD	7.47	10.25	12.33	12.37	13.19	12.51	12.89	14.00	14.49	14.87	13.78	13.20
2	(n)	24	24	24	24	24	24	24	24	24	24	24	24
	Mean	166.61	186.81	202.72	217.15	228.65	238.13	245.79	252.62	257.94	263.58	268.13	271.11
	SD	7.09	10.21	12.66	12.97	14.07	12.30	15.29	17.74	16.61	13.78	14.39	13.77
3	(n)	24	24	24	24	24	24	24	24	24	24	24	24
	Mean	166.56	188.51	205.52	219.84	227.97	236.49	244.54	250.05	256.56	261.67	269.05	269.78
	SD	7.05	8.95	11.60	13.29	12.34	13.62	15.42	15.84	13.91	16.10	15.20	17.37
4	(n)	32	32	32	32	32	32	32	32	31	31	31	31
	Mean	166.23	188.68	202.23	208.20	209.78**	215.43**	223.13**	228.57**	234.67**	240.34**	245.15**	246.01**
	SD	6.65	7.34	8.29	10.74	13.91	15.38	17.47	16.56	15.61	17.50	17.35	17.42

Note: ! = Pretest phase; " = Dosing phase
* = mean value of group is significantly different from control at $p < 0.05$
** = mean value of group is significantly different from control at $p < 0.01$
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are nonhomogeneous ($)

Table A.80(b)(iv) Body weight (in grams) of P females during gestation period in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group(s)		Day of Gestation 0	7	14	20
1	(n)	24	24	24	24
	Mean	271.12	291.86	319.43	389.72
	SD	14.77	12.01	13.26	34.03
2	(n)	21	21	21	21
	Mean	271.16	290.92	322.46	406.59
	SD	15.36	15.51	16.58	26.09
3	(n)	19	19	18	18
	Mean	270.15	290.85	321.70	402.88
	SD	14.80	21.02	20.18	30.29
4	(n)	26	26	26	26
	Mean	247.20**	264.86**($)	294.02**	357.94**
	SD	17.39	22.06	18.41	38.46

* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

Table A.80(b)(v) Body weight (in grams) of P females during post-partum period in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group(s)		Post - partum Day 0/1	4	7	14	21
1	(n)	24	22	21	21	21
	Mean	310.68	314.53	323.83	332.31	328.85
	SD	25.23	14.70	13.44	14.11	12.00
2	(n)	21	21	21	21	21
	Mean	314.73	321.34	327.15	341.14	338.32*($)
	SD	18.55	18.35	16.76	17.60	14.28
3	(n)	19	19	19	18	18
	Mean	316.87	316.17	321.45	335.91	334.55
	SD	22.31	21.84	22.39	20.81	19.69
4	(n)	26	26	26	26	26
	Mean	275.19**	281.86**	292.21**($)	307.90**($)	311.30**($)
	SD	26.32	26.27	25.77	25.94	21.57

* = mean value of group is significantly different from control at $p < 0.05$
** = mean value of group is significantly different from control at $p < 0.01$
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

Table A.80(b)(vi) Body weight (in grams) of F1 males in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group(s)		Nominal Day 28	35	42	49	56	63	70	77	84	91
1	(n)	24	24	24	24	24	24	24	24	24	24
	Mean	83.95	129.47	177.66	223.37	272.54	302.18	329.55	351.50	370.67	385.35
	SD	10.54	14.72	15.87	18.66	18.81	20.03	21.43	22.22	24.68	23.80
2	(n)	24	24	24	24	24	24	24	24	24	24
	Mean	78.06	121.66	170.63	217.83	265.78	295.64	323.25	344.24	363.85	378.15
	SD	11.17	14.75	17.36	18.30	20.53	21.85	23.13	25.51	26.32	26.16
3	(n)	24	24	24	24	24	24	24	24	24	24
	Mean	80.33	123.48	173.34	222.25	269.56	300.64	328.21	349.14	370.12	384.90
	SD	15.24	18.65	20.62	22.57	21.75	22.25	22.97	23.89	24.98	25.48
4	(n)	32	32	32	32	32	32	32	32	32	32
	Mean	73.37*	115.32**	164.67*	211.93	259.65	292.57	319.35	341.37	358.53	374.61
	SD	15.27	20.25	22.84	24.53	24.65	25.18	24.26	26.33	25.97	26.40

Group(s)		Nominal Day 98	105	112	119	126	133	140	147
1	(n)	24	24	24	24	24	24	24	24
	Mean	392.37	401.82	413.67	420.58	427.58	437.08	442.02	448.26
	SD	24.37	27.13	26.17	27.20	26.88	26.81	27.60	27.79
2	(n)	24	24	24	24	24	24	24	24
	Mean	386.03	395.97	406.46	417.43	423.26	430.14	435.45	442.81
	SD	26.75	29.16	29.05	31.60	32.51	31.53	32.00	31.66
3	(n)	24	24	24	24	24	24	24	24
	Mean	393.04	403.96	415.83	425.84	433.81	442.15	447.26	452.17
	SD	25.78	29.02	29.69	30.06	30.43	32.25	32.55	32.11
4	(n)	32	32	32	32	32	32	32	32
	Mean	384.89	391.51	403.34	409.57	414.88	423.69	426.77	433.51
	SD	23.73	25.13	25.82	27.73	28.63	28.97	30.67	31.88

Note: Data for Dosing phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

Table A.80(b)(vii) Body weight (in grams) of F1 females before pairing in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group(s)		Nominal Day 28	35	42	49	56	63	70	77	84	91
1	(n)	24	24	24	24	24	24	24	24	24	24
	Mean	75.65	111.06	143.50	165.78	187.71	202.02	215.61	228.19	238.01	245.37
	SD	9.92	10.62	10.01	10.89	10.90	11.37	12.21	15.38	14.33	13.43
2	(n)	24	24	24	24	24	24	24	24	24	24
	Mean	71.24	105.63	137.03	160.86	183.04	198.35	211.60	222.52	232.31	239.70
	SD	10.31	12.36	12.62	11.74	12.97	13.17	14.71	15.70	16.55	17.76
3	(n)	24	24	24	24	24	24	24	24	24	24
	Mean	70.24	104.45	139.36	164.51	186.94	203.70	216.29	226.33	236.68	242.06
	SD	12.80	14.30	15.51	13.39	14.63	14.50	13.78	15.23	16.52	15.42
4	(n)	32	32	32	32	32	32	32	32	32	32
	Mean	67.04*	101.87	135.45*($)	160.98	182.96	199.12	210.70	216.79*	223.09**	230.56**
	SD	14.45	17.67	17.66	16.37	16.78	18.31	18.71	21.47	21.15	20.20

Note: Data for Dosing phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

Table A.80(b)(viii) Body weight (in grams) of F1 females during gestation period in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group(s)		Day of Gestation 0	7	14	20
1	(n)	19	19	19	19
	Mean	241.26	260.48	292.17	368.55
	SD	13.45	11.67	12.87	19.97
2	(n)	15	15	15	15
	Mean	236.53	257.89	286.91	353.88
	SD	18.13	18.40	20.55	28.27
3	(n)	24	24	24	24
	Mean	242.68	263.90	294.83	370.02
	SD	16.41	16.40	17.86	22.82
4	(n)	28	28	28	28
	Mean	233.22	253.12	281.01	360.45
	SD	19.17	22.71	24.79	27.28

Note: Data for Gestation phase
* = mean value of group is significantly different from control at $p < 0.05$
** = mean value of group is significantly different from control at $p < 0.01$
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

Table A.80(b)(ix) Body weight (in grams) of F1 females during post-partum period in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group(s)		Post - partum Day 0/1	4	7	14	21
1	(n)	20	20	20	20	20
	Mean	286.92	297.93	300.25	308.52	307.70
	SD	25.17	13.21	19.02	22.61	18.16
2	(n)	15	15	15	15	15
	Mean	278.57	294.56	301.14	310.47	299.74
	SD	34.90	19.93	22.78	22.17	25.71
3	(n)	24	24	24	24	24
	Mean	303.10	292.65	302.74	318.44	310.92
	SD	29.80	20.25	16.12	16.26	15.57
4	(n)	28	28	28	28	27
	Mean	281.15	281.54*	289.29	304.66	296.89
	SD	33.30	24.23	22.79	23.25	22.45

* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

Table A.80(b)(x) Litter data at birth and on Day 4 post-partum of P generation in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group		At birth: Litter size Total	Litter size Live	Pup loss%	Litter wt.(g)	Mean pup wt.(g)	On Day 4: Live litter size	Cumul-ative loss%	Litter wt.(g)	Mean pup wt.(g)
1	(n)	22	22	22	22	22	21	21	21	21
	Mean	13.5	12.2	9.4	76.7	6.3	11.5	14.7	108.9	9.5
	SD	2.0	2.2	12.0	16.4	0.7	3.1	19.1	21.0	0.7
2	(n)	21	21	21	21	21	21	21	21	21
	Mean	13.1	11.9	9.2	75.9	6.4	11.6	11.0	110.1	9.5
	SD	1.5	1.5	11.3	11.0	0.3	1.7	12.8	17.7	0.8
3	(n)	19	19	19	19	19	19	19	19	19
	Mean	12.7	11.2	12.5	73.0	6.5	10.9	14.6	99.7	9.2
	SD	3.3	3.7	13.8	24.3	0.5	3.5	14.1	32.8	1.6
4	(n)	26	26	26	26	26	25	26	26	26
	Mean	11.6	10.7	8.2	68.9	6.4	10.1	14.9	95.1	9.5
	SD	3.6	3.9	15.2	25.1	0.6	4.1	20.2	36.7	1.7

* Statistically significantly different from control group value at p < 0.05
For reduction in (n) see Appendix 8

Table A.80(b)(xi) Litter data from Day 7 through Day 21 post-partum of P generation in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group		On Day 7: Live litter size	Pup loss %	Litter wt.(g)	Mean pup wt.(g)	On Day 14: Live litter size	Cumul-ative loss%	Litter wt.(g)	Mean pup wt.(g)	On Day 21: Live litter size	Cumul-ative loss%	Litter wt.(g)	Mean pup wt.(g)	Lactation index (%)
1	(n)	21	21	21	21	21	21	21	21	21	21	21	21	21
	Mean	7.6	0.0	112.8	14.8	7.5	1.2	228.3	30.4	7.5	1.2	364.7	48.6	98.8
	SD	1.2	0.0	20.8	1.3	1.3	5.5	40.2	1.8	1.3	5.5	64.5	3.1	5.5
2	(n)	21	21	21	21	21	21	21	21	21	21	21	21	21
	Mean	8.0	0.6	114.0	14.3	7.8	3.0	226.9	29.2	7.8	3.0	357.3	45.9	97.0
	SD	0.2	2.7	11.6	1.4	0.9	11.1	31.1	1.9	0.9	11.1	57.5	4.4	11.1
3	(n)	19	19	19	19	18	18	18	18	18	18	18	18	18
	Mean	7.4	1.8	103.5	13.6	7.6	2.8	215.8	27.8	7.6	3.5	330.9	43.1*	96.5
	SD	1.4	7.0	31.3	3.0	1.2	11.8	54.4	5.6	1.2	12.0	80.3	8.1	12.0
4	(n)	26	26	26	26	26	26	26	26	26	26	26	26	26
	Mean	7.0	0.5	100.0	14.2	7.0	0.5	189.8*	26.7*	7.0	0.5	285.6*	40.1*	99.5
	SD	1.9	2.5	29.2	2.2	1.9	2.5	59.3	4.2	1.9	2.5	91.6	6.8	2.5

* Statistically significantly different from control group value at p < 0.05
For reduction in (n) see Appendix 8

Table A.80(b)(xii) Litter data at birth and on Day 4 post-partum of F1 generation in the 2-generation reproduction toxicity study

(**Doc IIIA A6.8.2/02**)

Group		At birth: Litter size Total	Litter size Live	Pup loss%	Litter wt.(g)	Mean pup wt.(g)	On Day 4: Live litter size	Cumul-ative loss%	Litter wt.(g)	Mean pup wt.(g)
1	(n)	20	20	20	20	20	20	20	20	20
	Mean	13.4	12.8	4.7	78.9	6.2	12.4	7.1	113.2	9.1
	SD	2.5	2.4	5.1	15.0	0.3	2.4	8.1	24.9	1.1
2	(n)	15	15	15	15	15	15	15	15	15
	Mean	12.3	11.3	7.7	70.6	6.3	11.1	10.0	105.3	9.6
	SD	2.6	2.7	8.7	15.9	0.3	2.8	9.1	23.0	0.8
3	(n)	24	24	24	24	24	24	24	24	24
	Mean	12.8	11.8	7.3	74.3	6.4	10.8*	14.7	101.4	9.6
	SD	2.3	2.3	11.1	12.2	0.5	2.4	15.2	16.3	1.3
4	(n)	28	28	28	28	28	27	27	27	27
	Mean	13.7	12.9	7.5	80.6	6.3	13.1	6.4	115.5	8.9
	SD	2.7	2.9	15.9	17.4	0.3	1.8	7.5	15.0	0.6

* Statistically significantly different from control group value at p < 0.05

Table A.80(b)(xiii) Litter data from Day 7 through Day 21 post-partum of F1 generation in the 2-generation reproduction toxicity study (**Doc IIIA A6.8.2/02**)

Group		On Day 7: Live litter size	Pup loss %	Litter wt.(g)	Mean pup wt.(g)	On Day 14: Live litter size	Cumul-ative loss%	Litter wt.(g)	Mean pup wt.(g)	On Day 21: Live litter size	Cumul-ative loss%	Litter wt.(g)	Mean pup wt.(g)	Lactation index (%)
1	(n)	20	20	20	20	20	20	20	20	20	20	20	20	20
	Mean	8.0	0.0	109.2	13.7	7.9	1.3	225.8	28.7	7.9	1.3	367.6	46.7	98.7
	SD	0.2	0.0	18.3	2.2	0.5	4.1	30.3	2.8	0.5	4.1	47.6	4.3	4.1
2	(n)	15	15	15	15	15	15	15	15	15	15	15	15	15
	Mean	7.9	0.0	114.5	14.6	7.9	0.0	228.4	29.0	7.9	0.0	370.1	47.0	100.0
	SD	0.4	0.0	11.3	1.4	0.4	0.0	19.8	1.6	0.4	0.0	31.6	2.4	0.0
3	(n)	24	24	24	24	24	24	24	24	24	24	24	24	24
	Mean	7.9	0.0	110.6	14.1	7.7	2.7	211.9	27.6	7.6	3.2	334.2*	43.7	96.8
	SD	0.3	0.0	15.6	2.1	0.6	5.3	31.5	3.5	0.6	6.8	61.2	6.8	6.8
4	(n)	27	27	27	27	27	27	27	27	27	27	27	27	27
	Mean	8.0	0.5	98.4*	12.4*	8.0	0.5	195.9*	24.6*	8.0	0.5	285.1*	35.8*	99.5
	SD	0.2	2.4	13.2	1.6	0.2	2.4	28.0	3.5	0.2	2.4	54.5	6.9	2.4

* Statistically significantly different from control group value at p < 0.05

Table A.80 Summary table of human data on adverse effects on sexual function and fertility

No human data is available.

Table A.81 Summary table of other relevant studies for sexual function and fertility
No other data is available.

A3.10.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility
In the first study 2-generation reproduction toxicity study performed in accordance with GLP and US EPA 83-4 (Doc IIIA A6.8.2/01), rats were given 0.5, 1.5 and 3.5 (4.5 during first three weeks) mg NaPT/kg bw/day via oral gavage. At 3.5 mg/kg bw/day toxic changes were observed in both the parental animals and offspring. These were observed as reduction in body weight gain, atrophy of hind limb muscles with related hind limb paralysis/impairment of moment in some females, and adverse effects on only P generation fertility and mating performance. At 1.5 mg/kg bw/day, toxic changes in the parental animals were limited to atrophy of the hind limb muscles in a few females. At 0.5 mg/kg/day, no effects were seen in any group.

In the second 2-generation reproduction toxicity study performed in accordance with GLP and US EPA OPPTS 870.3800 (Doc IIIA A6.8.2/02), rats were given 0.7, 1.4 and 2.8 mg NaPT/kg bw/day via oral gavage. Reduced food consumption and body weight were observed in P and F1 adults together with emaciation in females of the highest dose group. Reduced kidney weight together with increased uterus weight were seen from 1.4 mg/kg bw/day in the P females while at 2.8 mg/kg bw/day an increased spleen weight was observed in the F1 females and lower epididymides weights were recorded in the F1 males together with slightly later preputial separation.

A3.10.1.2 Comparison with the CLP criteria
Adverse effects on sexual function and fertility are defined (Annex I: 3.7.1.3) as any effect of a substance that has the potential to interfere with sexual function and fertility including, but not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive system.

Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data or from animal data. The classification of a substance in Category 1A is largely based on evidence from humans. The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed 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 the other toxic effects.

In the first study there was statistically significant effects in the highest dose group on fertility and mating performance of the P generation and a non-dose dependent decrease in fertility indices was observed in the P generation of the second study. However, in both studies the observed effects were of low magnitude and only observed in the P generation, i.e. they were not reproducible within the studies. In addition, there were no effects on sperm motility, morphology or concentration observed or any other sign in these studies (organ weights or histopathological findings) of an adverse effect on male or female reproductive organs. No effect on litter size at birth was recorded in either study. Thus, the data available on sodium pyrithione are not considered to provide evidence of adverse effects on sexual function and fertility.

A3.10.1.3 Overall conclusion on sexual function and fertility related to risk assessment
Not applicable for the CLH report.

A.3.10.2. Developmental toxicity

Table A.82 Summary table of animal studies on adverse effects on development

Summary table of animal studies on adverse effects on development							
Method, Duration of exposure, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/ group	Test substance (including purity), Vehicle, Dose levels,	NOAELs, LOAELs (e.g. maternal, teratogenicity, embryotoxicity, offspring, parental, reproductive toxicity)	Results, maternal/parental (e.g. corrected body weight gain, for all dose levels)	Results, developmental (e.g. pup survival, structural abnormalities, altered growth, functional deficiencies, incidences and severity of the effects for all dose levels)	Remarks (e.g. major deviations)	Reference
PNDT, GD 6-19, Oral gavage, OECD 414, GLP: Yes, Reliability: 1, Key study	Rat Hsd: Sprague Dawley 24 females/	Sodium pyrithione (40.8% aqueous suspension, purity not specified),	NOAEL maternal and developmental : 2 mg/kg bw/day	<u>Dams – 4.0 mg/kg/day:</u> ↓ food consumption compared to controls (-20-28%, p<0.01) ↓ adjusted body weight compared to controls (-19%, p<0.01) ↓ mean gravid uterus weights compared to controls (-19%, p<0.01)	No effect on foetal viability was observed. <u>Foetuses – 4.0 mg/kg/day:</u> ↓ foetal weights compared to controls (-15%, p<0.05) ↑ number of small (<2.7g)	-	Doc IIIA A6.8.1/04 Year: 2001 (unpublish

	group Water, 0, 1, 2, 4 mg/kg bw		LOAEL maternal and developmental: 4 mg/kg bw/day	↑ number of animals having difficulty in movement (21 compared to 0 in controls) ↑ number of animals with impairment of hind limbs (7 compared to 0 in controls) ↑ number of animals with hunched posture (3 compared to 0 in controls) ↑ number of animals with emaciation (2 compared to 0 in controls)	foetuses (11.3% compared to 0.3% in controls) ↑ incidence of foetuses with incomplete ossifications: • 6th sternebrae (11.2% compared to 4.4% in controls) • metacarpals, no ossification (51% compared to 17.6% in controls) metatarsals, no ossification (7.7% compared to 2.2% in controls)		ed)
PNDT, GD 6-15, Dermal, No guideline, GLP: No, Reliability: 2 Supporting study	Rat, Charles River COBS® CD® 25 females/ group	Sodium pyrithione (purity: > 90%), Aquaphor® Cream 0, 0.5, 1.5, 3.0, and 7.0 mg/kg/day	NOAEL maternal and developmental: 3 mg/kg bw/day LOAEL maternal and developmental: 7 mg/kg bw/day	<u>Dams – 7 mg/kg/day:</u> ↓ body weight gain ($p<0.05$) ↑ deaths (5 animals) ↓ thymus weight ↑ fore limb and hind limb weakness (>50% of animals)	No effect on foetal viability was observed. <u>Foetuses – 7 mg/kg dose group:</u> ↓ foetus bodyweights (71% of control) Delayed ossification. Malformations observed included bent ribs (54 compared to 4 in control group) and limbs (19 compared to 0 in control group).	Application site was not washed off until after the last dose on GD 15.	Doc IIIA A6.8.1/05 Year: 1980 (unpublished)
PNDT, GD 6-19, Dermal, US EPA FIFRA 83-3 (similar to OECD 414), GLP: Yes, Reliability: 1	Rabbit, New Zealand White 20 females/ group	Sodium pyrithione (43.8% aqueous solution, purity not specified), Water, 0, 1.0, 2.5, and 5.0 mg/kg/day	NOAEL maternal: 2.5 mg/kg bw/day LOAEL maternal: 5 mg/kg bw/day NOAEL developmental: 5 mg/kg bw/day (highest dose)	<u>Dams – 5.0 mg/kg/day</u>: ↓ body weight gain compared to controls (-32-52%, not statistically significant).	No developmental toxicity or effects on foetal viability or foetal body weights were observed in any dose group.		Doc IIIA A6.8.1/06 Year: 1987 (unpublished)

2-generation reproduction toxicity study, Oral gavage, US EPA 83-4, GLP: Yes, Reliability: 1, Key study	Rat Crl:CD(SD)BR 25/sex/group	Sodium pyrithione (purity not specified; 41.2% aqueous solution), Water, 0, 0.5, 1.5, and 3.5 (4.5 during first three weeks) mg/kg bw, Starting 11 weeks before mating until sacrifice	NOAEL - parental: 0.5 mg/kg bw/day. LOAEL – parental: 1.5 mg/kg bw/day (atrophy of hind limb muscles in F1 females). NOAEL – offspring: 1.5 mg/kg bw/day LOAEL – offspring: 3.5 mg/kg bw/day (slight retardation of development during lactation).	<u>P animals – 3.5 mg/kg bw/day:</u> ↓ body weight (♀ and ♂) compared to control from week 3 throughout most of the study, including during gestation and lactation (ca -4-9%, p<0.01) ↑ atrophy of skeletal muscle fibres from the upper hind limb with related hind limb paralysis/impairment of movement (♂:8; ♀: 19) <u>F1 adults – 3.5 mg/kg bw/day:</u> ↑ mortality, 2 ♀ killed *in extremis* ↓ body weight gain, (♀: -9-11 %, p<0.0001, throughout gestation and lactation; ♂: -5%, p<0.05 but not statistically significant when compared individually ↓ food consumption at the pre-mating period (♀: -8%, p<0.01) ↑ atrophy of skeletal muscle fibres from the upper hind limb with related hind limb paralysis/impairment of movement (9 ♂ and 20 ♀) <u>F1 adults – 1.5 mg/kg bw/day:</u> ↑ atrophy of skeletal muscle fibres from the upper hind limb with related hind limb paralysis/impairment of movement (3 ♀)	<u>F1 pups – 3.5 mg/kg bw/day:</u> ↑ mortality (1♂ + 1♀) shortly after weaning, may have been due to gavage trauma ↓ pup body weights towards the end of lactation, particularly for females reaching statistical significance (p<0.05) from day 14 when compared on group basis but not individually. Compared to controls day 21: females -5%, males -1%. No difference was seen at birth. ↓ number of pups with startle response on day 15 (-10%, p<0.01) <u>F2 pups – 3.5 mg/kg bw/day:</u> ↓ pup body weights towards the end of lactation compared to controls (-5% in ♂ and -10% in ♀, not statistically significant)	Study is equivalent to OECD 416 with the following deviations amongst other: No organ weights; Number of implantations, corpora lutea and post implantation loss was not determined; Spinal cord and sciatic nerve were not subjected to histopathology.	Doc IIIA A6.8.2/01 Year: 1989 (unpublished)
2-generation reproduction toxicity study, Oral gavage, US EPA OPPTS 870.3800, GLP: Yes, Reliability: 1, Key study	Rat Hsd: Sprague Dawley 24/sex/group (plus 8 additional animals per sex in the high dose group)	Sodium pyrithione (purity not specified; 40.8% aqueous solution), Water, 0, 0.7, 1.4, 2.8 mg/kg bw, Starting 10 weeks before	NOAEL - parental: 0.7 mg/kg bw/day. LOAEL – parental: 1.4 mg/kg bw/day NOAEL – offspring: 0.7 mg/kg bw/day LOAEL – offspring:	<u>P animals – 2.8 mg/kg bw</u>: ↑ emaciation during weeks 1-17 (16 ♀) ↓ food consumption (♂: -6%, p<0.01; ♀: -8%, p<0.05, on gestation day 7-11-19%, p<0.01, post-partum days 14 and 21) ↓ body weights (♂: -5%, p<0.01, ♀: -9%, p<0.01, during pre-mating, gestation and post-partum periods from day 22) ↓ terminal body weights (♂+♀: -12%, p<0.01) <u>F1 adults – 2.8 mg/kg bw</u>: ↑ number of days taken for preputial separation (mean 45.38 compared to mean 44.17 in control, p<0.05) ↑ emaciation during nominal weeks 5-17 (5 ♀), ↓ body weights (-8-11% in ♂ on nominal days	<u>F1 pups – 2.8 and 1.4 mg/kg bw:</u> ↓ mean pup weight before/at weaning compared to controls (post-partum day 21 for mid-dose (-12%, p<0.05) and days 14 and 21 for high-dose (- 13-18%, p<0.05)) ↑ number of small pups (determined clinically) before weaning (15 (7.0%) in mid-dose and 24 (8.6%) in high-dose compared to 1 (0.4%) in controls) ↑ number of pups with testis not descended at	Deviations, amongst other: Only 10 random selected P and F1 adults were selected for histopathology while according to the guideline it should be	Doc IIIA A6.8.2/02 Year: 2003 (unpublished)

		mating until sacrifice	1.4 mg/kg bw/day (lower pup/litter weight, a number of pups with testis not descended in offspring of P and F1 animals).	28-42 (p<0.01), and -6% in ♀ (p<0.01) on nominal days 77-91) ↓ food consumption on nominal days 35 and 42, gestation days 7 and 14 and post-partum day 21 (- 6-12% in ♀, p<0.01)	weaning (5 in mid-dose and 6 in high-dose compared to 0 in control group) <u>F2 pups – 2.8 mg/kg bw:</u> ↓ pup weight post-partum days 7-21 (-10% day 7 and -24% day 21, p<0.05) ↑ testis not descended at weaning (10 compared to 3 in the control group) <u>F2 pups – 1.4 mg/kg bw:</u> ↑ pup loss post-partum day 4 (-13%, p<0.05). No effects observed in high dose. ↓ litter weight compared to controls post-partum day 21 (-10%, p<0.05)	for all animals of the high dose and control group. Furthermore, the previously identified target organs skeletal muscle, sciatic nerve and spinal cord were not investigated.	

Table A.83(a)(i) Maternal effects in the PNDT oral rat study (**Doc IIIA A6.8.1/04**)

Parameter	**control data**		**low dose**	**medium dose**	**high dose**	**dose-response + / -**
	historical	study				
Number of dams examined	not reported	24	24	24	24	no
Clinical findings during application of test substance: difficulty in movement, impairment of hindlimbs, hunched posture, emaciation.	/	-	-	-	+	+
Mortality of dams (%)	/	0	0	0	0	no
Abortions (%)	/	0	0	0	0	no
Body weight gain Day 3 Day 6 Day 9 Day 12 Day 15 Day 18 Day 20	/	-	-	-	 - - ↓ ↓ ↓ ↓ ↓	+

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
Food consumption Day 3 Day 6 Day 9 Day 12 Day 15 Day 18 Day 20	/	-	-	-	 - - ↓ - - ↓ ↓	+
Water consumption	/	n.a.	n.a.	n.a.	n.a.	n.a.
Pregnancies (No. / %)	/	23	23	22	22	no
Unilateral implantations	/	0	0	1	0	no
Litters with live foetuses	/	23	23	22	22	no
Necropsy findings in dams dead before end of test	/	n.a.	n.a.	n.a.	n.a.	n.a.

n.a.: not available or not applicable.

Table A.83(a)(ii) Litter response (Caesarean section data) in the PNDT oral rat study (**Doc IIIA A6.8.1/04**)

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
Corpora lutea	not reported	15.52	15.00	14.82	14.95	no
Implantations. mean per litter	not reported	15.09	14.74	14.32	14.41	no
Early uterine deaths. mean per litter	not reported	0.65	0.57	0.77	0.95	no
Late uterine deaths. mean per litter	not reported	0.35	0.09	0.00	0.23	no
Total uterine deaths. mean per litter	not reported	1.04	0.65	0.77	1.18	no
Viable young. mean per litter	not reported	14.04	14.09	13.55	13.23	no
Percent males	not reported	48.29	49.83	48.36	46.59	no
Preimplantation loss (%)	not reported	2.67	1.61	3.36	3.62	no
Postimplantation loss (%)	not reported	7.39	4.43	5.64	8.16	no

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
Total implantation loss (%)	not reported	9.76	5.95	8.80	11.42	no
Litter weight (g)	not reported	52.12	51.63	50.13	42.09	+
Mean foetal weight (g)	not reported	3.74	3.66	3.70	3.18	+
placenta weight (mean) [g]	not reported	not reported	not reported	not reported	not reported	n.a.

n.a.: not applicable.

Table A.83(a)(iii) Examination of the foetuses in the PNDT oral rat study (**Doc IIIA A6.8.1/04**)

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
External anomalies / malformations	not reported					+
Number of foetuses examined		323	324	298	291	
Number of litters examined		23	23	22	22	
Number of foetuses with no abnormalities detected (%)		322 (99.7)	320 (98.8)	293 (98.3)	256 (88)	
No of small foetuses (< 2.7 g)		1	4	5	33	
[The incidence of other abnormalities was 0 or 1 in each group.]						
Malformations:						
umbilical hernia		0	1	0	0	
anus imperforate		0	0	0	1	

Parameter	**control data**		**low dose**	**medium dose**	**high dose**	**dose-response + / -**
	historical	study				
Visceral anomalies / malformations Number of foetuses examined Number of litters examined Number of foetuses with no abnormalities detected (%) Number of litters with no abnormalites detected (%) [The incidence of the various abnormalities detected varied between 0 and 23, without any dose dependence, see Table 10 of the report.]	not reported	 157 23 121 (77.1) 23 (100)	 157 23 123 (78.3) 23 (100)	 143 22 115 (80.4) 22 (100)	 142 22 108 (76.1) 22 (100)	no
Skeletal anomalies / malformations Number of foetuses examined Number of litters examined Number of foetuses with no abnormalities detected (%) Number of litters with no abnormalites detected (%) [The incidence of incomplete ossification of sternebrae, metacarpals and metatarsals was increased in the high dosed group, see Table 11 of the report. The other findings were scattered over the groups and were not dose dependent.]	not reported	 136 19 66 (48.5) 16 (84.2)	 147 20 57 (38.8) 18 (90)	 132 19 74 (56.1) 16 (84.2)	 143 21 31 (21.7) 12 (57.1)	+

Table A.83(a)(iv) Clinical signs of females (group incidence) in the PNDT oral rat study (**Doc IIIA A6.8.1/04**)

Interval: 0 - 20 Days Group Observation	1 (24)		2 (24)		3 (24)		4 (24)	
	a	b	a	b	a	b	a	b
No significant signs	24	100.0	24	100.0	24	100.0	24	100.0
BEHAVIOUR - ACTIVITY								
Difficulty in movement	0	0.0	0	0.0	0	0.0	21	87.5
Impaired hindlimb(s)	0	0.0	0	0.0	0	0.0	7	29.2
APPEARANCE								
Staining Urogenital region	1	4.2	0	0.0	0	0.0	1	4.2
Hunched posture	0	0.0	0	0.0	0	0.0	3	12.5
Emaciated	0	0.0	0	0.0	0	0.0	2	8.3
Hairloss	0	0.0	1	4.2	0	0.0	1	4.2
EYE - EAR - MOUTH								
Teeth cut	24	100.0	24	100.0	24	100.0	24	100.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Percent of animals with observation during interval

Table A.83(a)(v) Body weight gain per day (gms) of pregnant females (group mean data) in the PNDT oral rat study (**Doc IIIA A6.8.1/04**)

Group(s)		Day of Gestation 3	6	9	12	15	18	20
1	(n)	23	23	23	23	23	23	23
	Mean	5.472	3.786	3.401	5.067	7.170	14.250	16.086
	SD	2.325	1.894	0.976	0.854	1.364	2.181	3.870
2	(n)	23	23	23	23	23	23	23
	Mean	5.345	3.906	3.525	5.401	7.113	13.714	16.897
	SD	1.758	1.191	1.394	1.214	1.798	1.492	3.451
3	(n)	22	22	22	22	22	22	22
	Mean	6.024	3.591	2.603	5.045	6.259	13.041	13.952
	SD	1.641	1.207	1.527	1.667	1.942	2.520	4.010
4	(n)	22	22	22	22	22	22	22
	Mean	5.488	3.745	0.106**	5.655	3.675**($)	3.704**($)	4.429**($)
	SD	1.216	1.491	1.509	1.752	3.029	6.577	6.361

°= mean daily body weight gain over the previous period starting from gestation Day 0
* = mean value of group was significantly different from control at $p < 0.05$
** = mean value of group was significantly different from control at $p < 0.01$
Statistical analysis: Dunnett's test if group varianaces are homogeneous
: Modified t test if group variances are inhomegeneous ($)

Table A.83(a)(vi) Food consumption (gms/animal/day) of pregnant females (group mean data) in the PNDT oral rat study (**Doc IIIA A6.8.1/04**)

Group(s)		Day of Gestation 3	6	9	12	15	18	20
1	(n)	9	9	9	9	9	9	9
	Mean	22.50	22.32	22.01	25.04	24.35	27.42	26.87
	SD	3.70	3.21	1.52	2.00	1.89	2.90	3.39
2	(n)	8	8	8	8	8	8	8
	Mean	22.93	22.13	21.53	24.41	26.36	28.17	29.31
	SD	3.79	3.29	1.00	1.34	2.62	2.80	2.66
3	(n)	9	9	9	9	9	9	9
	Mean	23.28	22.81	20.17*	23.77	24.95	27.81	30.13
	SD	2.80	3.74	1.85	2.31	2.40	3.44	7.97
4	(n)	9	9	9	9	9	9	9
	Mean	23.13	21.85	17.73**	22.89	23.18	19.80**	19.76**($)
	SD	3.57	3.13	1.49	2.17	1.56	3.37	3.15

° = food consumed over the previous period
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

Table A.83(b)(i) Maternal effects in the PNDT dermal rat study (**Doc IIIA A6.8.1/05**)

Parameter	**control data**		**Grp 0.5**	**Grp 1.5**	**Grp 3.0**	**Grp 7.0**
	historical	**Grp 0**				
Number of dams examined	not reported	25	26	25	25	20
Clinical findings during application of test substance: difficulty in movement, impairment of hind limbs, hunched posture, emaciation.	/	-	-	-	-	+
Mortality of dams (%) (Both females dying on-study appeared normal, gained weight, and no adverse clinical signs were apparent – deaths not believed related to test article)	/	0	1[1]	0	0	5
Abortions (%)	/	0	0	0	0	0

Parameter	control data		Grp 0.5	Grp 1.5	Grp 3.0	Grp 7.0
	historical	Grp 0				
Body weight gain Day 6 Day 9 Day 12 Day 16 Day 20	/	 - - - - -	 - - - - -	 - - - - -	 - - - - -	 - ↓ ↓ ↓ ↓
Water consumption	/	n.a.	n.a.	n.a.	n.a.	n.a.
Pregnancies (No. / %)	/	23	22	19	24	20
Litters with live foetuses	/	22	22	19	24	19
Necropsy findings in dams dead before end of test	/	n.a.	No adverse findings.	n.a.	n.a.	No adverse findings

[1] Animal died prior to dosing, not test article related.
n.a.: not available or not applicable.

Table A.83(b)(ii) Litter response (Caesarean section data) in the PNDT dermal rat study (**Doc IIIA A6.8.1/05**)

Parameter	control data		Grp 0.5	Grp 1.5	Grp 3.0	Grp 7.0
	historical	Grp 0				
Corpora lutea	not reported	16.7	17.7	16.6	16.2	17.1
Implantations. mean per dam	not reported	14.4	15.4	13.5	15.2	14.4
Early Resorptions. mean per dam	not reported	1.2	0.9	0.7	1.1	1.1
Late Resorptions. mean per dam	not reported	0.0	0.0	0.0	0.0	0.7
Viable young. mean per dam	not reported	13.2	14.5	12.8	14.1	12.6
Male:Female ratio	not reported	158:146	160:158	114:129	173:165	121:131
Mean foetal weight (g)	not reported	3.8	3.7	3.7	3.7	2.7
placenta weight (mean) [g]	not reported	not reported	not reported	not reported	not reported	not reported

Table A.83(b)(iii) Examination of the foetuses (major findings) in the PNDT dermal rat study (**Doc IIIA A6.8.1/05**)

Parameter	control data		Grp 0.5	Grp 1.5	Grp 3.0	Grp 7.0
	historical	Grp 0				
External anomalies / alterations	not reported					
Number of foetuses examined		304	318	243	338	252
Number of litters examined		22	22	19	24	19
Total number of foetuses with malformation (number of litters)		7 (5)	8 (5)	1 (1)	3 (2)	57 (16)
Eyes opened - Fetus (litters)		-	2 (1)	-	-	-
Cleft palate – fetus (litters)		-	1 (1)	-	1 (1)	1 (1)
Limb anomalies – fetus (litters)		-	-	1 (1)	-	19 (7)
Rib anomalies – fetus (litters)		7 (5)	2 (2)	1 (5)	-	54 (14)
Variations	not reported					
14th Rudimentary rib(s) – fetus (litter)		34 (15)	28 (8)	35 (12)	43 (14)	11 (5)
Reduced ossification of skull – fetus (litter)		10 (6)	6 (2)	3 (2)	3 (3)	51 (12)
Sternebrae #5 &/or #6 unossified – fetus (litter)		12 (6)	22 (10)	14 (11)	18 (9)	75 (14)

Table A.83(b)(iv) Group mean maternal body weights and body weight change in the PNDT dermal rat study (**Doc IIIA A6.8.1/05**)

	Vehicle Control 0 mg/kg/day	Aristocort® Positive Control 0.03 ml/day	Sodium Omadine® (mg/kg/day)			
			0.5	1.5	3.0	7.0
Day of Gestation	Group Mean Maternal Body Weight (grams)					
0	274	276	280	277	279	276
6	301	300	307	298	306	305
9	300	292	300	301	300	289
12	313	293	318	318	318	306
16	335	294	342	342	339	271
20	405	335	416	407	405	297
Days of Gestation	Group Mean Maternal Body Weight Change (grams)					
0- 6	27	24	27	21	27	29
6- 9	-1	-8	-7	3	-6	-16
9-12	13	1	18	17	18	17
12-16	22	1	24	24	21	-35
16-20	70	41	74	65	66	26
6-16	34	-6	35	44	33	-34
6-20	104	35	109	109	99	-8
0-20	131	59	136	130	126	21

Table A.83(c)(i) Maternal effects in the PNDT dermal rabbit study (**Doc IIIA A6.8.1/06**)

Parameter	**control data**		**low dose**	**medium dose**	**high dose**	**dose-response + / -**
	historical	study				
Number of dams examined	not reported	20	20	20	20	-

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
Clinical findings during application of test substance: Irritation Hair loss Staining: haircoat, nose Lacrimation Limb-impaired function Decreased defecation Material in pan	 - - - - - - -	 - 19 1 - - - -	 - 7 2 2 2 1 -	 - 11 - - - 2 1	 - 14 1 - - 2 -	 - - - - - ± -
Mortality of dams (%)	/	0	0	0	0	No
Abortions (%)	/	0	0.05	0	0	No
Body weight gain Day 3 Day 6 Day 9 Day 12 Day 15 Day 18 Day 20	/	-	-	-	 - ↓ ↓ ↓ ↓ ↓ ↓	+
Food consumption	/	n.a.	n.a.	n.a.	n.a.	n.a.
Water consumption	/	n.a.	n.a.	n.a.	n.a.	n.a.
Pregnancies (No. / %)	/	17	18	17	18	No
Unilateral implantations	/	0	0	0	0	No
Litters with live foetuses	/	16	17	17	18	No
Necropsy findings in dams dead before end of test	/	n.a.	n.a.	n.a.	n.a.	n.a.

n.a.: not available or not applicable.

Table A.83(c)(ii) Litter response (Caesarean section data) in the PNDT dermal rabbit study (**Doc IIIA A6.8.1/06**)

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
Corpora lutea (per doe)	not reported	12	11.8	11.0	10.6	No
Implantations. mean per litter	not reported	7.4	6.7	7.3	6.4	No
Early uterine deaths. mean per litter	not reported	1	1	0	0	No
Late uterine deaths. mean per litter	not reported	0.8	0.9	0.5	0.4	No
Total uterine deaths. mean per litter	not reported	1.8	1.9	0.5	0.4	No
Viable young. mean per litter	not reported	6.6	5.7	6.8	6.1	No

Parameter	**control data**		**low dose**	**medium dose**	**high dose**	**dose-response + / -**
	historical	study				
Percent males	not reported	51.3	55.3	44.0	54.1	No
Pre-implantation loss (%)	not reported	34.9	41.3	33.7	38.9	No
Post-implantation loss (%)	not reported	10.3	14.2	6.5	6.0	No
Total implantation loss (%)	not reported	45.2	55.5	40.2	44.9	No
Litter weight (g)	not reported	-	-	-	-	-
Mean foetal weight (g)	not reported	43.4	45.1	43.8	45.6	No
placenta weight (mean) [g]	not reported	not reported	not reported	not reported	not reported	n.a.

n.a.: not applicable.

Table A.83(c)(iii) Examination of the foetuses in the PNDT dermal rabbit study (**Doc IIIA A6.8.1/06**)

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
Malformations Number of foetuses examined Number of litters examined Total number of foetuses (number of litters) with malformations	not reported	113 16 8 (6)	103 17 10 (8)	116 17 2 (2)	109 18 3 (3)	-
Visceral anomalies Number of foetuses examined Number of litters examined Total number of foetuses (number of litters) with variations	not reported	113 16 88 (16)	103 17 80 (17)	116 17 84 (17)	109 18 72 (18)	No

Table A.83(c)(iv) Group mean maternal body weights and body weight change in the PNDT dermal rabbit study (**Doc IIIA A6.8.1/06**)

Day of Gestation	0 (Control)		1		2.5		5	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0	3460	202.2	3531	235.3	3382	218.9	3362	258.5
6	3606	200.8	3675	219.0	3519	250.9	3520	246.0
13	3727	187.1	3768	234.4	3608	258.3	3578	241.1
20	3935	205.4	3932	229.0	3791	271.6	3720	242.6
24	4046	226.1	4003	274.3	3881	245.4	3831	302.6
29	4037	251.4	4058	283.6	3892	290.5	3890	289.7
Days of Gestation	Group Mean Maternal Body Weight Changes (grams)[a]							
0 to 6	146	57.2	144	69.3	137	74.6	158	43.2
6 to 13	121	103.5	93	56.5	89	75.2	58	76.0
13 to 20	209	62.6	164	108.5	183	58.8	142	117.8
20 to 24	111	74.5	71	151.4	91	103.4	111	119.4
24 to 29	-9	115.0	26	78.3	11	144.2	59	114.1
6 to 20[b]	329	113.0	257	90.5	272	97.1	200	141.4
0 to 29	577	177.2	535	174.6	510	149.0	528	142.8

a: Values represent the mean of the individual changes in maternal body weight for these intervals.
b: Gestation day 20 weights were utilized to reflect the 14-day treatment regimen.
S.D.: Standard deviation.

Table A.83 Summary table of human data on adverse effects on development
No human data is available.

Table A.84 Summary table of other relevant studies for developmental toxicity

Summary table of other relevant studies for developmental toxicity				
Type of data/report, Reliability, Key/supportive study	Test substance (including purity), Vehicle	Relevant information about the study	Main effects, Observations	Reference
Rat whole embryo culture assay (rWEC), Reliability: 1, Supporting study.	Sodium pyrithione (purity not specified), Vehicle: Tyrode's Buffer	Rat embryos (18-24/treatment) were harvested on gestational day 9 and cultured for approximately 44 hours. The embryos were incubated with vehicle (0.02%) or 0.15, 0.46, 0.92 or 2.3 µM NaPT. Embryos were evaluated by visual assessment and an in-house scoring system to identify and grade the degree of severity of morphological abnormalities. The percent incidence of dysmorphogenesis (defined as possessing morphological scores ≤ 3 in any	NaPT was found to be negative in the assay.	Daston et al., 2017a (in manuscript)

		given endpoint) was also calculated.		
Rat whole embryo culture assay, Reliability: 1, Supporting study.	Principle metabolite of sodium pyrithione: 2-(methylsulfonyl)pyridine (2-MSP) (purity not specified), Vehicle: Tyrode's Buffer	Rat embryos (13-15/treatment) were harvested on gestational day 9 and cultured for approximately 44 hours. The embryos were incubated with vehicle (0.02%) or 3, 6, 12 or 30 µM NaPT. Embryos were evaluated by visual assessment and an in-house scoring system to identify and grade the degree of severity of morphological abnormalities. The percent incidence of dysmorphogenesis (defined as possessing morphological scores ≤ 3 in any given endpoint) was also calculated.	2-MSP was found to be negative in the assay.	Daston et al., 2017b (in manuscript)

Table A.85(a) Summary of the results of rWEC assay with NaPT (2-marcaptopyridine-N-oxide sodium salt) (Daston et al., 2017a, in manuscript)

Test Group	Dose Level [µM]	Embryo Number [a]	CR Length Mean (SD) [mm]	Somite Number Mean (SD)	Yolk Sac Mean (SD)	TMS[a] Mean (SD)	Incidence of Dysmor-phogenesis [%]
Tyrodes	0.02%	22	**3.0** (0.1)	**22.8** (1.3)	**4.9** (0.4)	**34.3** (0.5)	5
2-Mercaptopyridine-N-oxide sodium salt	0.15	24	**3.0** (0.2)	**22.6** (1.3)	**4.8** (0.5)	**33.3** (1.2)	21
	0.46	22	**2.9** (0.4)	**21.5** (5.4)	**4.5** (0.7)	**30.4** (4.9)	50
	0.92	18	**3.1** (0.1)	**23.8** (2.0)	**4.6** (0.5)	**33.4** (1.3)	22
	2.3	22	**3.1** (0.1)	**23.8** (1.0)	**4.9** (0.3)	**33.6** (0.6)	9

[a]TMS – total morphological score (determined by summing rotation, caudal, neural tube, primitive spinal cord, pharyngeal arch, face and heart score values). Abbreviations: CR – crown rump; SD – standard deviation.

Table A.85(b) Summary of the results of rWEC assay with 2-MSP (the primary metabolite of NaPT) (Daston et al., 2017b, in manuscript)

Test Group	Dose Level [µM]	Embryo Number[a]	CR Length Mean (SD) [mm]	Somite Number Mean (SD)	Yolk Sac Mean (SD)	TMS[a] Mean (SD)	Incidence of Dysmor-phogenesis [%]
Tyrode's	0.02%	13	**3.3** (0.2)	**22.7** (1.4)	**4.8** (0.4)	**34.5** (0.2)	8
2-(Methylsulfonyl) pyridine	3.0	14	**3.1** (0.2)	**23.2** (1.5)	**4.8** (0.4)	**34.5** (0.4)	0
	6.0	15	**3.3** (0.3)	**23.6** (0.9)	**5.0** (0.0)	**34.6** (0.1)	0
	12.0	14	**3.0** (0.1)	**22.5** (1.3)	**4.8** (0.4)	**34.4** (0.7)	0
	30.0	13	**3.2** (0.2)	**23.9** (1.6)	**4.8** (0.4)	**34.2** (0.5)	0

[a]TMS – total morphological score (determined by summing rotation, caudal, neural tube, primitive spinal cord, pharyngeal arch, face and heart score values). Abbreviations: CR – crown rump; SD – standard

A3.10.2.1 Short summary and overall relevance of the provided information on adverse effects on development

In a pre-natal developmental toxicity (PNDT) study performed according to OECD 414 and with GLP, NaPT was given to rats (24 females/group) via oral gavage during gestation days 6-19 at doses of 0, 1, 2, and 4 mg/kg bw/day (Doc IIIA A6.8.1/04). Maternal toxicity was observed in the high-dose group in the form of reduced food consumption, body weight gain and gravid uterus weights. There was an increase in number of animals having difficulty in movement, impairment of hind limbs, hunched posture or with emaciation. There were no effects on foetal viability at the high-dose but the foetal weights were decreased, an increased number of small foetuses and an increased incidence of foetuses with incomplete ossifications was observed.

In a PNDT study not conforming to any guideline or GLP, NaPT was administered dermally to rats (25 females/group) during gestation days 6-15 at doses of 0, 0.5, 1.5, 3, and 7 mg/kg bw/day (Doc IIIA A6.8.1/05). NaPT was applied to the shaven backs but there was no attempt to remove the test article until 24 hours after the very last dose on gestation day 15. The high dose of 7.0 mg/kg/day proved to be excessively high as 5 females died during the study with severe reductions in bodyweight gain for all females in this group. Fore limb and hind limb weakness was also noted in the majority of the animals and several females had reduced thymus weight. Foetotoxicity was observed in the high-dose group in the form of decrease in foetal bodyweight and delayed ossification; and malformations such as bent ribs and bent limb bones. No developmental toxicity or malformations were observed in any of the foetuses from any of the other doses. Signs of dermal irritation were observed at the site of application in all treatment groups with the 0.5 mg/kg group showing only slight irritation.

In another PNDT study performed according to US EPA FIFRA 83-3 (similar to OECD 414) and GLP, NaPT was administered dermally for 6 hrs per day (the skin was then washed with water and blotted dry) to New Zealand White rabbits (20 females/group) during gestation days 6-19 at doses of 0, 1, 2.5, and 5 mg/kg bw/day (Doc IIIA A6.8.1/06). The only sign of toxicity was a depressed bodyweight gain (- 32 to 52%) observed in the high-dose group. There was no developmental toxicity or effects on foetal viability or foetal body weights in any of the dose groups. It is stated in the full study report that the dose-levels in this study were set based on a range-finding study wherein premature death and excessive maternal weight loss was observed at 7.5, 15 and 30 mg/kg bw/day. The DS does not have access to the range-finding study.

In a 2-generation reproduction toxicity study performed in accordance with GLP and US EPA 83-4 (Doc IIIA A6.8.2/01), rats were given 0, 0.5, 1.5, and 3.5 (4.5 during first three weeks) mg NaPT/kg bw/day via oral gavage. At 3.5 mg/kg bw/day toxic changes were observed in both the parental animals and offspring. These were observed as reduction in body weight gain, atrophy of hind limb muscles with related hind limb paralysis/impairment of moment in some females, and adverse effects on only P generation fertility and mating performance. In the offspring, there was evidence of a slight retardation of development during lactation. At 1.5 mg/kg bw/day, toxic changes in the parental animals were limited to atrophy of the hind limb muscles in a few females, with no effects on the offspring. At 0.5 mg/kg bw/day, no effects were seen in any group.

In another 2-generation reproduction toxicity study performed in accordance with GLP and US EPA OPPTS 870.3800 (Doc IIIA A6.8.2/02), rats were given 0, 0.7, 1.4, and 2.8 mg NaPT/kg bw/day via oral gavage. Reduced food consumption and body weight were observed in F0 and F1 adults together with emaciation in females of the highest dose group. Reduced kidney weight together with increased uterus weight were seen from 1.4 mg/kg bw/day in the F0 females while at 2.8 mg/kg bw/day increased spleen weight was observed in the F1 females and lower epididymides weights were recorded in the F1 males together with slightly later preputial separation. There was a significantly decreased weight of the pups in the F1 and F2 generations, an increased loss of pups in the F2 generation on day 4 post-partum and increased presence of pups with testis not descended after exposure to 1.4 mg/kg bw/day or higher.

In two rat whole embryo culture (rWEC) assays, the embryos harvested on gestation day 9 and cultured for approximately 44 hours were incubated with sodium pyrithione and 2-MSP, the principle metabolite of pyrithione, at concentrations of 0.15, 0.46,

0.92 or 2.3 µM and 3, 6, 12 or 30 µM, respectively. Embryos were evaluated by visual assessment and an in-house scoring system to identify and grade the degree of severity of morphological abnormalities. The percent incidence of dysmorphogenesis (defined as possessing morphological scores ≤ 3 in any given endpoint) was also calculated. Both NaPT and 2-MSP were negative in the assays. There were sporadic effects observed in the assays with NaPT, however, there was no dose-response and lack of effects at the highest concentration.

A3.10.2.2 Comparison with the CLP criteria

Adverse effects on development of the offspring (Annex I: 3.7.1.4) includes any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or post-natally, to the time of sexual maturation. As classification for developmental toxicity is primarily intended to provide a hazard warning for pregnant women and for men and women of reproductive capacity, for pragmatic purposes, classification for developmental toxicity is essentially intended to encompass adverse effects induced during pregnancy, or as a result of parental exposure.

Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data or from animal data. The classification of a substance in Category 1A is largely based on evidence from humans. The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on development and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed 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 the other toxic effects.

The reduction in foetal weights and incomplete ossifications in the oral and dermal rat PNDT studies or the reduced pup body weights and retardation of development during lactation in the two 2-two generation studies with sodium pyrithione could probably be explained by the maternal toxicity observed in those studies. The only significant effect such as the irreversible effects in the form of structural malformations (bent ribs and limbs) in the dermal rat PNDT study was observed at a dose-level that had 20% mortality. Thus, the data available on sodium pyrithione are not considered to provide evidence of adverse effects sufficient for classification

for development.

A3.10.2.3 Overall conclusion on effects on development related to risk assessment
Not applicable for the CLH report.

A.3.10.3. Effects on or via lactation

Table A.85 Summary table of animal studies on adverse effects on or via lactation

Summary table of animal studies on adverse effects on or via lactation						
Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/ group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	NOAEL, LOAEL	Results	Remarks (e.g. major deviations)	Reference
2-generation reproduction toxicity study, Oral gavage, US EPA 83-4, GLP: Yes, Reliability: 1, Key study	Rat Crl:CD(SD)BR 25/sex/group	Sodium pyrithione (purity not specified; 41.2% aqueous solution), Water, 0, 0.5, 1.5, and 3.5 (4.5 during first three weeks) mg/kg bw, Starting 11 weeks before mating until sacrifice	NOAEL – offspring: 1.5 mg/kg bw/day LOAEL – offspring: 3.5 mg/kg bw/day (slight retardation of development during lactation).	<u>F1 pups – 3.5 mg/kg bw/day:</u> ↑ mortality (1♂ + 1♀) shortly after weaning, may have been due to gavage trauma ↓ pup body weights towards the end of lactation, particularly for females reaching statistical significance ($p<0.05$) from day 14 when compared on group basis but not individually. Compared to controls day 21: females -5%, males -1%. No difference was seen at birth. ↓ number of pups with startle response on day 15 (-10%, $p<0.01$) <u>F2 pups – 3.5 mg/kg bw/day:</u> ↓ pup body weights towards the end of lactation compared to controls (-5% in ♂ and -10% in ♀, not statistically significant)	-	Doc IIIA A6.8.2/01 Year: 1989 (unpublished)
2-generation reproduction toxicity study, Oral gavage, US EPA OPPTS 870.3800,	Rat Hsd: Sprague Dawley 24/sex/group (plus 8 additiona	Sodium pyrithione (purity not specified; 40.8% aqueous solution), Water, 0, 0.7, 1.4, 2.8	NOAEL – offspring: 0.7 mg/kg bw/day LOAEL – offspring: 1.4 mg/kg bw/day (lower pup/litter	<u>F1 pups – 2.8 and 1.4 mg/kg bw:</u> ↓ mean pup weight before/at weaning compared to controls (post-partum day 21 for mid-dose (-12%, $p<0.05$) and days 14 and 21 for high-dose (- 13-18%, $p<0.05$)) ↑ number of small pups (determined clinically) before weaning (15 (7.0%) in mid-dose and 24 (8.6%) in high-dose compared to 1 (0.4%) in controls) ↑ number of pups with testis not descended at weaning (5 in mid-dose and 6 in high-dose compared to 0 in control group)	-	Doc IIIA A6.8.2/02 Year: 2003 (unpublished)

GLP: Yes, Reliability: 1, Key study	l animals per sex in the high dose group)	mg/kg bw, Starting 10 weeks before mating until sacrifice	weight, a number of pups with testis not descended in offspring of P and F1 animals).	<u>F2 pups – 2.8 mg/kg bw:</u> ↓ pup weight post-partum days 7-21 (-10% day 7 and -24% day 21, p<0.05) ↑ testis not descended at weaning (10 compared to 3 in the control group) <u>F2 pups – 1.4 mg/kg bw:</u> ↑ pup loss post-partum day 4 (-13%, p<0.05). No effects observed in high dose. ↓ litter weight compared to controls post-partum day 21 (-10%, p<0.05)		

Table A.86 Summary table of human data on adverse effects on or via lactation
No human data is available.

Table A.87 Summary table of other relevant studies for adverse effects on or via lactation
No other data is available.

A3.10.3.1 Short summary and overall relevance of the provided information on effects on or via lactation
In the first study 2-generation reproduction toxicity study performed in accordance with GLP and US EPA 83-4 (Doc IIIA A6.8.2/01), rats were given 0.5, 1.5 and 3.5 (4.5 during first three weeks) mg NaPT/kg bw/day via oral gavage. In the offspring, there was evidence of a slight retardation of development during lactation. In both the F1 and F2 generations: pup body weights were slightly lower than controls toward the end of lactation; the number of pups exhibiting some developmental landmarks by certain days was reduced (not statistically significant) compared with the controls; a slight reduction (not statistically significant) in the number of pups born. However, in the high-dose group there was statistically significant decreased body weight gain in P females on post-partum Days 0, 7, and 14 (see Table A.80(a)(iii) above) and in F1 females on post-partum Days 0, 7, 14, and 21 (see Table A.80(a)(v) above). Moreover, there was atrophy of skeletal muscle fibres from the upper hind limb muscle with related hind limb paralysis/impairment of movement in the P (19 in the high-dose) and F1 (20 in the high-dose and 3 in the mid dose) females.

In the second 2-generation reproduction toxicity study performed in accordance with GLP and US EPA OPPTS 870.3800 (Doc IIIA A6.8.2/02), rats were given 0.7, 1.4 and 2.8 mg NaPT/kg bw/day via oral gavage. There was a significantly decreased weight of the pups in the F1 and F2 generations, an increased loss of pups in the F2 generation on day 4 post-partum and increased number of pups with testis not descended after exposure of 1.4 mg/kg bw/day or higher. However, there was statistically significant decreased body weight gain in the high-dose P females on post-partum Days 0, 4, 7, and 14 (see Table A.80(a)(v) above) but only on post-partum Day 4 in high-dose F1 female (see Table A.80(b)(ix) above). Moreover, the previously identified target organs (skeletal muscle, sciatic nerve and spinal cord) were not investigated in this study.

A3.10.3.2 Comparison with the CLP criteria

Adverse effects on or via lactation are included under reproductive toxicity, but for classification purposes such effects are treated separately (Annex I: 3.7.1.5). Substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the basis of:

(a) human evidence indicating a hazard to babies during the lactation period; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

There is no human evidence indicating a hazard to babies during lactation or ADME studies indicating that sodium pyrithione may be present in potentially toxic levels in breast milk. Statistically significant decreases in pup body weights were observed in both the two-generation studies with sodium pyrithione in rats mainly during the latter part of the lactation period. The magnitude of the decrease in body weight ranged from 5% in one study to 10-24% in the other study. However, in the presence of maternal toxicity or incomplete investigation of know target organs, the DS considers that there is no clear evidence of adverse effects on or via lactation.

A3.10.3.3 Overall conclusion on effects on or via lactation related to risk assessment
Not applicable for the CLH report.

A3.10.4 Conclusion on classification and labelling for reproductive toxicity
Based on the substance-specific data, the DS proposes no classification for adverse effects on sexual function and fertility, on development or on or via lactation for sodium pyrithione according to the CLP criteria.

A3.10.5 Overall conclusion on reproductive toxicity related to risk assessment
Not applicable for the CLH report.

A.3.11. Aspiration hazard

Table A.88 Summary table of evidence for aspiration hazard
No data is available.

A3.11.1 Short summary and overall relevance of the provided information on aspiration hazard
No data is available.

A3.11.2 Comparison with the CLP criteria
No data is available.

A3.11.3 Conclusion on classification and labelling for aspiration hazard
No data is available.

A.3.12. Neurotoxicity

Table A.89 Summary table of animal studies on neurotoxicity
See Section A.3.7 Repeated dose toxicity/STOT RE.

Table A.90 Summary table of human data on neurotoxicity
No human data is available.

A3.12.1 Short summary and overall relevance of the provided information on neurotoxicity
See Section A.3.7 Repeated dose toxicity/STOT RE.
A3.12.2 Comparison with the CLP criteria
See Section A.3.7 Repeated dose toxicity/STOT RE.
A3.12.3 Conclusion on neurotoxicity related to risk assessment
Not applicable for the CLH report.

A.3.13. Immunotoxicity

Table A.91 Summary table of in vitro immunotoxicity studies
No in-vitro data is available.

Table A.92 Summary table of animal studies on immunotoxicity
No animal data is available.

Table A.93 Summary table of human data on immunotoxicity
No human data is available.

A3.13.1 Short summary and overall relevance of the provided information on immunotoxicity
No relevant data is available.

A3.13.2 Comparison with the CLP criteria
Not applicable.

A3.13.3 Conclusion on immunotoxicity related to risk assessment
Not applicable for the CLH report.

A.3.14. Endocrine disruption

Table A.94 Summary table of in vitro studies on endocrine disruption
No *in vitro* data is available.

Table A.95 Summary table of animal data on endocrine disruption
No animal data is available.

Table A.96 Summary table of human data on endocrine disruption
No human data is available.

Table A.97 Summary table of other evidence on endocrine disruption
No other data is available.

A.3.15. Further Human data

Table A.98 Summary table of further human data
No further human data is available.

A.3.16. Other data

Table A.99 Summary table of other data
No further data is available.

A.4. Environmental effects assessment

A.4.1. Fate and distribution in the environment

A.4.1.1. Degradation

A4.1.1.1 Abiotic degradation
Hydrolysis

Table A.100 Summary table - Hydrolysis

Summary table - Hydrolysis							
Method, Guideline, GLP status, Reliability, Key/supportive study	pH	Temp. [°C]	Initial TS concentration, C_0 [mg/l]	Half-life, DT50 [d]	Coefficient of correlation, r2	Remarks	Reference
Federal Register Vol. 50, No. 188 (Friday 27, 1985) Rules and Regulations, p. 39252.	3	25	140 NaPT	Infinite	N.a.	[-]	Doc III A7.1.1.1.1/01 Year: 1996
	7						
	11						

Doc III A7.1.1.1.1/01, 1996

Sodium pyrithione (NaPT) was tested at a very high concentration 140 mg/l. The hydrolysis rate was zero at pH 3, 7, and 11 during 28 days.

Summary

The hydrolysis rate of sodium pyrithione is low or zero (at high test concentrations; 140 mg/l). No hydrolysis products were identified at pH 3, 7 and 11.

Phototransformation in water

Table A.101 Summary table – Photolysis in water

Summary table – Photolysis in water							
Method, Guideline, GLP status, Reliability, Key/supportive study	Initial TS concentration.	Total recovery of test substance [% of appl. AS]	Photolysis rate constant (kcp)	Direct photolysis sunlight rate constant (kpE)	Reaction quantum yield (φcE)	Half-life (t1/2E)	Reference
Similar to the requirements of OPPTS 835.2210 and OPPTS 830.7050	1 µg NaPT/L	Not reported	Not reported	Not reported	0.15	Not reported	Doc III A7.1.1.1.2/03 Year: 2005
US FDA Techn. Assist. Doc, Guideline 3.10 Photodegr. 1987	10 mg NaPT/L	Not reported	pH 5: 0.12 pH 7: 0.16	[-]	[-]	[-]	Doc III A7.1.1.1.2/01 Year: 1996

Doc III A7.1.1.1.2/03, 2005, RI = 1-2
The study was conducted to determine the influence of concentration on photolysis rates. Photolysis was investigated for sodium pyrithione, zinc pyrithione, and copper pyrithione in deionized water with concentrations of 0.1–1 µg/l, which are much closer to predicted environmental concentrations than those of many older studies are. Quartz tubes with the test substance were exposed to natural sunlight (42°N latitude) at noon during July through October. Four experiments with each substance were performed.

Pyrithione had considerable absorptivity in the range of 290–400 nm, where photoactive solar radiation is available.

Photolysis in deionized water in natural sunlight indicated half-lives ($t_{½E}$; as defined in OPPTS 835.2210) around 3.7–33 minutes, depending on the weather conditions and which pyrithione was studied. Simultaneous exposure of the actinometer (o-nitrobenzaldehyde) solutions allowed the calculation of photolysis disappearance quantum yields. Reproducibility at the concentration used in this study required that several exposure experiments were run for each test compound and the results were averaged. The quantum yield (Φ^{c}_{E}) for sodium pyrithione was 0.15 (n = 4).

The higher photolysis rate observed in the experiment with low concentration of pyrithione (µg/l) call for explanations. The distribution of pyrithione species (free pyrithione ion, $CuPT^{+}$, $Cu(PT)_{2,}$ $ZnPT^{+}$, HPT^{-} et cetera) may differ at different total pyrithione concentrations. The free form of pyrithione seems to be most susceptible for photoreaction.

The reaction quantum yield was highest for sodium pyrithione and lowest for copper pyrithione. This is in accordance with the free pyrithione being more sensitive to photolysis. The Dossier Submitter (DS) note that there is clearly an uncertainty associated with the quantum yield, as it may be dependent on the species pattern (Burns 2000, pages 48–50), and hence the value determined in pure water on the lab may not represent environmental conditions where copper and zinc ions may be available for binding with pyrithione.

Doc III A7.1.1.1.2/01, RI = 2.

The pyrithione concentration was not measured in a reliable manner. Some information on formation of degradation products can be found.

Summary

The studies above are performed with artificial water, which are free from suspended particles. Binding to organic matter decrease photoreactions for many chemicals, probably as a result of that the light photons do not reach molecules sorbed inside particles, but may also increase the quantum yield, and the summed effect is complicated (Schwarzenbach et al., 2003, pages 649–650; Burns LA, 2000[11]). Based on the laboratory studies the phototransformation of pyrithione in water is relatively rapid. However, due to various local conditions it is difficult to estimate the actual photochemical degradation rate in the environment.

[11] Schwarzenbach RP, Gschwend PM, Imboden DM. 2003. Environmental organic chemistry. John Wiley & Sons. Inc., New Jersey 1313 pp. and Burns LA. 2000. Exposure analysis modeling system (EXAMS): user manual and system documentation. US EPA report EPA/600/R - 00/081, September 2000, revision G (May 2004).

Estimated photo-oxidation in air

Calculations according to the Atkinson calculation method indicates a half-life of 53.8 hours for sodium pyrithiones (Doc III A7.3.1/01, 2007). The rates are based on the assumption of OH radical concentration of 1.5×10^6 (radicals)/$cm^{3,}$ which is 3 times higher than what is suggested in the TGD (part II, section 2.3.6.3). This means that rates would be three times slower if TGD values were applied, in essence a half-life of 160 hours for sodium pyrithione. The reliability for this study is only considered to be 3 (Klimisch score) as the results are based on calculations instead of data. However, due to limited availability of data for NaPT the results are still considered important for the conclusion on photo-oxidation in air.

A4.1.1.2 Biotic degradation

A4.1.1.2.1 Biodegradability (ready/inherent)

Table A.102 Summary table - biodegradation studies (ready/inherent)

Summary table - biodegradation studies (ready/inherent)										
Method, Guideline, GLP status, Reliability, Key/supportive study	Test type[1]	Test parameter	Inoculum			Additional substance	Test sub-stance concentr.	Degradation		Reference
			Type	Concen-tration	Adaptation			Incubation period	Degree [%]	
OECD guideline 301B	Ready	CO2 evolution	Activated sludge	30 mg dry material per litre	No	No	NaPT 30.2 mg/l (5 mg TOC/l)	28 d	0% after 6 d 24% after 20 d 79% after 28 d "Ready biodegradable"	Doc III A7.1.1.2.1/04 Year: 2002 RI = 1
OECD guideline 301B	Ready	CO_2 evolution	Activated sludge	30 mg dry material per litre	No	No	NaPT (aq. solution) c. not rep. (10 mg TOC/l)	43 d	2% after 8 d 60% after 18 d 70% after 43 d "Ready biodegradable"	Doc III A7.1.1.2.1/01 Year: 1998 Acceptable
OECD guideline 301B	Ready	CO_2 evolution	Activated sludge	30 mg dry material per litre	No	No	PSA 26.5 mg/l (10 mg TOC/l)	29 d	49% after 6 d 64% after 14 d 73% after 28 d "Ready	Doc III A7.1.1.2.1/03 Year: 2002 RI = 1

									biodegradable”	

In a study (Doc III A7.1.1.2.1/04, 2002) with sodium pyrithione, the substance was “readily biodegradable” under the conditions of OECD 301B.

Sodium pyrithione was also tested as an aqueous liquid solution (Doc III A7.1.1.2.1/01, 1998). The results showed 2 % degradation after 8 days, 60 % degradation after 18 days, 70 % after 43 days. A lag period of circa 6 days was observed, this was seen in spite of the fact that the sewage inoculum came from a treatment plant, which predominantly treats domestic waste, and therefore could be expected to be adapted to pyrithione background. However, in the test for inhibitory properties, sodium pyrithione was non-inhibitory as defined by the guideline (OECD 31 B, §25). A degradation plateau was attained at approximately Day 28. These results indicate that sodium pyrithione is readily biodegradable.

The major non-transient metabolite, pyridine sulphonic acid (PSA), was “readily biodegradable” and “not inhibitory” under the conditions of OECD 301B (Doc III A7.1.1.2.1/03, 2002).

Summary

Based on the available studies with NaPT and PSA, the results point toward readily biodegradable both for the substance NaPT and the most stable of the degradation products, PSA.

A4.1.1.3 Rate and route of degradation including identification of metabolites and degradation products

A4.1.1.3.1 Biological sewage treatment
Not applicable for CLH report.

A4.1.1.3.2 Biodegradation in freshwater
No information for sodium pyrithione available.

A4.1.1.3.3 Biodegradation in seawater
No information for sodium pyrithione available.

A4.1.1.3.4 Higher tier degradation studies in water or sediment
No higher tier degradation tests are available for sodium pyrithione.

A4.1.1.3.5 Biodegradation during manure storage
Not applicable for CLH report.

A4.1.1.3.6 Biotic degradation in soil
No information for sodium pyrithione available.

A4.1.1.3.7 Laboratory soil degradation studies
No information for sodium pyrithione available.

A4.1.1.3.8 Higher tier degradation studies in soil
No information for sodium pyrithione available.

A4.1.1.3.9 Short summary and overall relevance of the provided information on degradation and conclusion on rapid degradation

Two studies with NaPT and one study with PSA are available for assessment of inherent biodegradability. Both the substance sodium pyrithione and the degradation product PSA were concluded to be readily biodegradable based on these studies.

A.4.1.2. Distribution

A4.1.2.1 Adsorption onto/desorption from soils

Table A.103 Summary table – Adsorption/desorption

Summary table – Adsorption/desorption							
Method, Guideline, GLP status, Reliability	Soil	Ka	KaOC	Kd	KdOC	Remarks	Reference
OECD 106	Silty loam	260	11000	390	16000	RI = 1-2	Doc III A7.2.3.1/01 Year: 2002 (OECD 106)
	Clay loam	1800	51000	3800	110000		
	Loam	340	11000	550	18000		

	Clay	91	3500	190	7300		10–100 mg/l NaPT
	Sand	410	80000	1400	270000		

Ka = Adsorption coefficient (l/kg dw at 1 mg/l)
KaOC = Adsorption coefficient based on organic carbon content (l/kg OC at 1 mg/l). OC assumed = OM/1.7
Kd = Desorption coefficient
KdOC = Desorption coefficient based on organic carbon content
Ka/ Kd = Adsorption / Desorption distribution coefficient

Doc III A7.2.3.1 /01, 2002 (NaPT study)
Sorption of sodium pyrithione (10–100 mg/l) to five European soils was studies using the isotherm test (OECD 106). At these levels, toxicity to microorganisms may prevent degradation of the test substance. If it is the case, the sorption data, can be said to be less influenced by degradation, and apply for the parent substance.

DS found significant relations of the 10-logarithm of OC-normalised Freundlich adsorption- and desorption coefficients ("log KOC" at 1 mg/l) with soil pH.

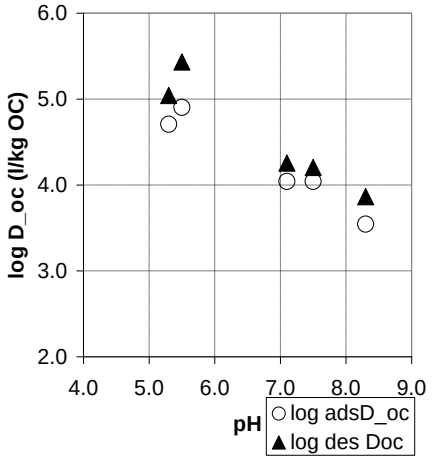


Figure 4.1.2.1-1. Adsorption and desorption log D_{OC} versus pH. Pyrithione added as 14C-labelled sodium pyrithione. Nominal test concentration 10–100 mg/l.

(A7.2.3.1/01, 2002)

A4.1.2.2 Higher tier soil adsorption studies

No higher-tier soil adsorption tests are available for sodium pyrithione.

A4.1.2.3 Volatilisation
Regarding volatilisation, please see Part A, section 1.3 Physical and chemical properties of the active substance.

A.4.1.3. Bioaccumulation

According to studies performed with sodium pyrithione and the shake-flask method the log K_{OW} for sodium pyrithione is approximately –1 to –2.64, please see section A.1.3 in the present report. The low log K_{OW} indicates low bioaccumulation potential. Sodium pyrithione is also readily degradable and will therefore probably not bioaccumulate.

Summary

Sodium pyrithione has a low potential to bioaccumulate.

A.4.1.4. Monitoring data

Not applicable for CLH report.

A.4.2. Effects on environmental organisms

A.4.2.1. Atmosphere

Not applicable for CLH report.

A.4.2.2. Toxicity to sewage treatment plant (STP) microorganisms

Inhibition of microbial activity (aquatic)

Two studies performed on sodium pyrithione are available.

Table A.104 Summary table – inhibition of microbial activity

Summary table – inhibition of microbial activity								
Method, Guideline, GLP status, Reliability, Key/supportive study	Species/ Inoculum	Endpoint	Duration	Results			Remarks	Reference
				NOEC	EC10 (µg/l)	EC50 (µg/l)		
OECD 209 NaPT	Activated sludge	Respiration inhibition	3 hrs		0.48 (EC_{20})	1.81	Nominal RI = 3	Doc III A7.4.1.4/01 Year: 2002
OECD 209 NaPT	Activated sludge	Respiration inhibition	3 hrs		1.0	120	Nominal RI = 3	Doc III A7.4.1.4/02 Year: 1990

Inhibition of microbial activity (aquatic)
In two studies the effect of sodium pyrithione on microbial activity in sewage was assessed by determining the respiration inhibition level of microorganisms in activated sludge according to OECD 209. There are no tests on the metabolites. The two tests performed with sodium pyrithione resulted in an EC50 of 1.8 – 120 mg/l after 3 hours exposure time. The results are based on nominal

concentration as no monitoring of the test substance was performed.

Summary

Overall there are indications that sodium pyrithione has a low to moderate acute toxic effect towards microorganisms in sewage treatment systems with an EC50 = 1.8 - 120 mg/l (nominal) based on the available studies. However, DS has given the studies a reliability of 3 (due to that the test substance was not measured and missing information on storage of stock solution), which means it is difficult to draw any conclusions only based on these studies. No NOEC was obtained from the study.

A.4.2.3. Aquatic compartment

A.4.2.3.1. Freshwater compartment

Acute/short-term toxicity (freshwater)

The summaries and evaluations of the acute aquatic studies with sodium pyrithione (NaPT) and metabolites are inherited from the substance evaluations, performed by the Swedish Chemicals Agency under BPR 528/2012, of the pyrithiones Copper, Zinc and Sodium Pyrithione. The Reach registration dossier has been reviewed and two additional studies performed with NaPT (one invertebrate study and one algae study) that were not previously included in the evaluation under BPR have been added as supporting data in the table over NaPT studies below. Furthermore, one additional study is available from the Art. 95 dossier (BPR Art. 95 dossier, 2015). For all of the three taxonomic groups (fish, invertebrates and algae), acute toxicity test with NaPT are available (see Table A.105). Only studies performed with the substance NaPT is included in the table below. However, additional studies performed with NaPT metabolites are presented in tables A4.2.3.1.1- 04 to 06, A4.2.3.1.2-01 to 03 and A4.2.3.1.3-01 to 03.

Table A.105 Summary table – acute/short-term aquatic toxicity

Summary table – acute/short-term aquatic toxicity										
Method, Guideline, GLP status, Reliability, Key/supportive	**Species**	**Endpoint/ Type of test**	**Test material**	**Exposure**		**Results**			**Remarks** (RI set by Reach registrant in brackets	**Reference**
				Design	Duration	NOEC (mg/l)	LC/EC10	LC/EC50 (mg/l)		

study									)	
Fish										
US EPA - 540/9-85-006	Fresh water *Oncorhyncus mykiss*	Mortality and signs of toxicity	NaPT	Flow through	96 h	1 (tox) 1.800 (mort.)		1.3	Nominal values RI=3 Supportive (RI = 1)	Doc III A7.4.1.1/01 Year: 1996
US EPA-FIFRA, 72-1 (comparable to OECD 203)	Fresh water *Salmo gairdneri*	Mortality	NaPT	Flow through	96 h	0.005		0.0073 (measured)	Nominal RI = 2-3 (RI = 1)	Doc III A7.4.1.1/02 Year : 1988
US EPA-FIFRA, 72-1 (comparable to OECD 203)	Fresh water *Lepomis Macrochirus*	Mortality	NaPT	Flow through	96 h	1.25		8.6 (measured)	Nominal RI = 3 (RI = 1)	Doc III A7.4.1.1/03 Year: 1987
OECD 203 GLP	Fresh water *Danio rerio*	Mortality	NaPT	Flow through	96 h			0.00767	Measured RI = 2 **(Key)**	BPR Art. 95 dossier Year: 2015 Unpublished
Invertebrates										
OECD 202 GLP	Fresh water *Daphnia magna*	Immobilisation	NaPT	Static	48 h	0.020		0.150	Nominal RI = 3 (RI = 1)	Doc III A7.4.1.2/01/ Smyth et al., Year: 1994
Not clear	Fresh water *Daphnia magna*	Immobilisation		Not reported	48 h	0.0115		0.0220	Nominal RI = 3	Doc III A7.4.1.2/02/ Anonymous

									(RI = 2)	Year: 1976
OECD 202 GLP	Fresh water *Daphnia magna*	Immobilisation	NaPT	Static	48 h	0.18		0.6	(RI = 1) The DS does not have the full study report.	REACH registration dossier, JS member, Opt-out Year: 2002
Algae (growth inhibition)										
OECD 201 GLP	Freshwater algae *Selenastrum capricornutum*	Growth inhibition	NaPT	Static	72 h	0.080r 0.040b		0.460r 0.230b	Nominal RI = 2 (RI = 1)	Doc III A7.4.1.3/01 Year: 1994
OECD 201 GLP	Freshwater algae *Desmodesmus subspicatus*	Growth inhibition	NaPT	Static		0.033r		0.22r	Measured (RI = 1) The DS does not have the full study report.	REACH registration dossier, JS member, Opt-out Year: 2002

r = inhibition based on growth rate, b = inhibition based on biomass

A4.2.3.1.1 Acute toxicity to fish

From Doc IIIA, (three studies):

Three tests are carried out with sodium pyrithione. A LC50 value based on nominal values is only reported in one of the studies (EC50 > 1 mg/l, DOCIII A7.4.1.1/01). However, the Klimisch reliability score for the study is considered to be 3. The study Doc III A7.4.1.1/02, 1988, RI = 2-3, resulted in a nominal concentration for NOEC approximately 200 times lower than the two other studies. Due to lack of a description of the analytical method used to determine the concentration of sodium pyrithione, the nominal

values are primarily adopted by the DS before measured values. The measured LC50 value presented in the Reach registration dossier is however also included in the table for information. The same hesitation applies to the measured values from the study DOC III A7.4.1.1./03 due to e.g. too high limit of detection (1 mg/l) in the analytical method used. The measured LC50 (average of two series) is however inserted in the table for information.

The measured LC50-value in study Doc III A7.4.1.1/02, 1988, is in agreement with the measured LC50-value study submitted with the BPR Art. 95 dossier, 2015, see details below.

(Interpretation of test results in the Reach-registration dossier. DOCIIIA7.4.1.1/02: NOEC 0.0026 mg/l)

BPR Art. 95 dossier, 2015 Unpublished (**Key**)

Guidelines followed:
OECD guideline 203 for Testing of Chemicals (1992), and Method C.1 of Commission Regulation (EC) No 440/2008 (2008).

Summary
The fish were exposed to the test item for 96 hours and mortalities were recorded at 24, 48, 72 and 96 hours. After 96 hours 6 out of 7 fish were dead at the highest test concentration, but before that no mortality was recorded for any of the test concentrations. The LC50 was calculated by linear regression based on the concentrations causing 0 and 86 % mortality. The LC50 was concluded to be 7.67 (5.43 – 9.79) µg NaPT/l. No DOC III summary exists for this study. Therefore, a more extensive description of the test is given below.

Method
Seven fish (*Danio rerio*) per test concentration were used in a flow-through study in freshwater.
The fish is reported to be in average 2.9 cm long at study start, which is within the recommended length (2.0 +/- 1.0) according to the guideline. However, the individual lengths were not reported so whether there were large differences in length or not is not known. Holding of the fish for acclimatisation was performed at the test laboratory during 12 days before the start of the test. Light conditions were the same during holding as during the actual test: a photoperiod of 16 hours per day and a light-intensity of 7-750 Lux. The hardness and pH were according to guideline. The temperature was as recommended for the test species and the oxygen saturation was kept at 100 % throughout the test.
Test concentrations were decided based on a preliminary range finding test, which showed no mortality at the nominal test item concentration of 2.44 µg/l and 100 % mortality at the test item concentration of 24.4 µg/l. For the definitive test the nominal test item concentrations: 2.45, 4.36, 7.75, 13.8, and 24.5 µg/l were included. Analytical evaluation of the various concentrations of the test items and the control was carried out via LC-MS/MS on study day -3, study day 0 and daily thereafter until end of exposure.
The chemical characterisation of the test item is stated to be an aqueous solution of sodium pyrithione. Information on purity of the substance NaPT is lacking. The bonding places of the chelating agent pyrithione were saturated with 4-Fluoro-7-nitro-2,1,3-benzoxadiazole (NBD-F) to form specific derivatives prior to the chromatographic analysis. This was done in order to avoid metal complexes, which could have influenced the chromatographic properties.

The transitions of the test item at m/z of 110.93 Da and 186.21 Da were selected as quantifier and qualifier ion traces of the test item respectively. The results from the method validation indicated sufficient accuracy. Mean recoveries, at the three different concentrations (5 replicates per concentration) 1 x LOQ, 10 x LOQ and 20 x LOQ, were 109 %, 83 %, and 104 %, respectively. The corresponding coefficients of variation were ≤ 5.0 % and a sufficient precision of the analytical method was concluded. Chromatograms for the blanks showed no response for the test substance or a response ≤ 30 % of LOQ, which indicates specificity.

Results
The measured concentrations of the test substance in the test vessels were in the range of 42 to 112 % of the nominal value during exposure. As the measured concentrations deviate more than 20 % from the nominal values the results are based on the arithmetic mean of the measured values in accordance with the guidance.

Maximum measured concentration causing no mortality within the period of the test is 13.3 µg/l (test item). No test concentration gave 100 % mortality. One fish was still alive at the highest measured test concentration 24 µg/l (test item) after 96 h, which corresponds to 86 % mortality (see table 7 below). The LC50 was therefore calculated by linear regression based on the concentrations causing 0 and 86 % mortality. No confidence value could be obtained, however, the result for the LC50 is also given as a range. From the linear regression, a LC50 for the test item of 18.8 µg/l was obtained. The range for the LC50 for the test item is 13.3 – 24.0 µg/l. In a certificate of analysis investigating the content of NaPT in the test item a concentration of 40.8 % NaPT was concluded. Therefore, the corresponding result for NaPT is:
LC50 = 7.67 (5.43 – 9.79) µg NaPT/l.

See below the mortality results for all test concentrations and the control and further down the linear regression used to calculate the LC50.

Table: A4.2.3.1.1-01 Observations of effected fish per test item concentration.

Arithmetic mean measured test item concentration [µg/L]	Observation *)	Number of fish affected after different exposure periods [hours]				
		2	24	48	72	96
24.0	(E)	-	-	-	-	6
	(2.5)	-	7	3	2	-
	(2.2)	-	-	-	2	-
	(2.1)	-	-	4	3	1
	(1)	7				
13.3	(2.5)	-	-	-	-	5
	(2.3)	-	-	-	-	1
	(2.1)	-	-	-	-	1
	(1)	7	7	7	7	-
6.59	(1)	7	7	7	7	7
3.05	(1)	7	7	7	7	7
1.35	(1)	7	7	7	7	7
Control	(1)	7	7	7	7	7

*) The number in the brackets correspond to the following observation:

(1) = Normal behaviour
(E) = Exitus lethalis
(2.1) = Lethargy
(2.2) = Side position
(2.3) = Staggering
(2.5) = Missing escape reflex
- = Not observed

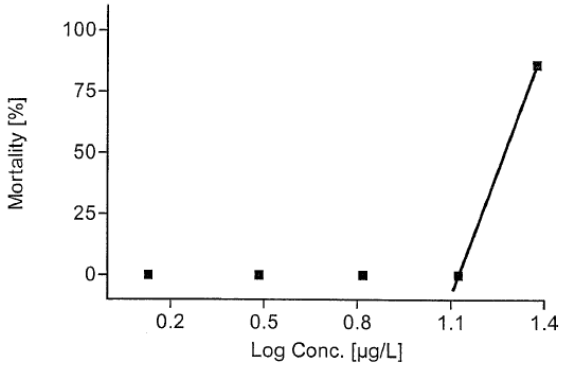


Figure 1: **Concentration - Effect Relationship after 96 hours**
(based on arithmetic mean measured test item concentrations)

Figure A4.2.3.1.1-01 Linear regression of % mortality verses logged test item concentrations.
Y(mortality) = Slope x log(x) + Yintercept

Tables A4.2.3.1.1-02/03 Fitting results for the linear regression shown in figure A4.2.3.1.1-01.

Log Conc. [µg/L]	Mortality [%]
0.130	0.000
0.484	0.000
0.819	0.000
1.124	0.000
1.380	86.000

Fitting Results:

	Mortality [%]
Straight line, with ECx antilog	Perfect fit
Best-fit values	
YIntercept	-377.0
Slope	335.5
EC10	14.24
EC20	15.26
EC50	18.75
Std. Error	
YIntercept	
Slope	
95% Confidence Intervals	
YIntercept	
Slope	
EC10	
EC20	
EC50	
Goodness of Fit	
Degrees of Freedom	0
R square	1.000
Absolute Sum of Squares	0.0
Sy.x	
Number of points	
Analyzed	2

Reliability and Acceptability

SE CA give the report a reliability of 2. The study is well reported and conducted in accordance with the guideline. The range finding test was somewhat misguiding and had the test concentrations been set at bit higher a more robust result might have been obtained. However, the results are still considered sufficiently reliable and the result is in agreement with the results presented in Doc III A7.4.1.1/02 (1988). The results from the study are acceptable for classification purpose.

Metabolites

Tables A4.2.3.1.1-04 Acute toxicity of pyridine-N-oxide-2-sulfonic acid to fish ("OMSoA"/"OMSA") to fish

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results [mg/l]		Reference
			design	duration	NOEC	LC50	
US EPA-72-1	Freshwater *Pimephales promelas*	Mortality	Flow-through	96 h	48.7	>48.7	Doc III A7.4.1.1/17 Year: 1994 RI = 3 Acceptable for test concentrations with acceptable pH.
US EPA-72-3 (b)	Marine *Cyprinodon variegatus*	Mortality	Flow-through	96 h	137	>137	DOC III A7.4.1.1/14 Year: 1994 RI = 2
US-EPA-72-1	Freshwater *Oncorhyncus mykiss*	Mortality	Flow-through	96 h	18	>73.6	DOC III A7.4.1.1/11 Year: 1994 RI = 3 Acceptable, but not for the highest concentration.

Tables A4.2.3.1.1-05 Acute toxicity of pyridine sulphonic acid to fish ("PSA" or "PSoA")

Guideline / Test method	Species	Endpoint / Type of test	Exposure design	duration	Results [mg/l] NOEC	LC50	Reference
US EPA-72-1	Freshwater *Pimephales promelas*	Mortality	Flow-through	96 h	55.2	>55.2	Doc III A7.4.1.1/18 Year: 1994 RI = 3 Acceptable for the test conc with acceptable pH.
US EPA-72-1	Freshwater *Oncorhyncus mykiss*	Mortality	Flow-through	96 h	28.5	>46.9	Doc III A7.4.1.1/12 Year: 1993 RI = 2
US EPA-72-3 (b)	Marine *Cyprinodon variegates*	Mortality	Flow-through	96 h	127	>127	Doc III A7.4.1.1/15 Year: 1994 RI = 2

Tables A4.2.3.1.1-06 Acute toxicity of 2,2'-(pyridyl-N-oxide) disulphide to fish ("OMDS")

Guideline / Test method	Species	End-point / Type of test	Exposure design	duration	Results [mg/l] NOEC	LC50	Reference
US EPA-72-1	Freshwater *Pimephales promelas*	Mortality	Static renewal (every 24 h)	96 h	0.011 (nom)	0.030 (nom)	Doc III A7.4.1.1/16 Year: 1995 RI = 3 due to nominal concentrations, but acceptable for classification purpose.

US EPA-72-1	Freshwater *Oncorhyncus mykiss*	Mortality	Flow-through	96 h	0.018	0.054	Not summarised Year: 1995 (Reach reg RI = 1)
US EPA-72-3 (b)	Marine *Cyprinodon variegates*	Mortality	Static renewal (every 24 h)	96 h	<0.52 (nom)	1.1 (nom)	Doc III A7.4.1.1/13 Year: 1995 RI = 2

Metabolites: Aquatic toxicity tests with fish and pyrithione metabolites.

Acute toxicity tests for organic metabolites were submitted. The results from the tests show that pyrithione disulphide (OMDS) is the most toxic of the studied metabolites, followed by PSA (2-pyridinesulfonic acid) and OMSA (2-pyridine-N-oxide sulfinic acid). However, since pyrithione disulphide probably is very short-lived in the environment, the more stable PSA is considered to be the most environmentally relevant metabolite. From the fate studies on degradation, many metabolites were identified, but the only one persistent enough to give exposure above a 10 % level was PSA. For OMDS, some experimental indications on a half-life for OMDS was found in the various ecotoxicity studies (Doc IIIs: A7.4.1.1/13, 1995; A7.4.1.1/16, 1995; A.7.4.1.2/10; A7.4.1.2/16, A7.4.1.3/10; A7.4.1.2/13). In the study reports, a half-life of OMDS is claimed to be "2.5 minutes" but without any support for that. SE CA therefore made own estimates of the persistence of OMDS, which indicate a single-first order dissipation half-life of 9–53 hours (0.4–2.2 days) in various aquatic ecotoxicity test systems. Based on an outdoor water-sediment microcosm fate experiment (Doc III A7.1.2.2.2/08, 2006), a very rough estimate of dissipation half-life of OMDS was 22 minutes (two data points first 2 hours).

In a number of the tests (Doc IIIs: A7.4.1.1/17, A7.4.1.1/11, A7.4.1.1/18, A7.4.1.1/12), the pH in aquaria with higher concentration of test substance was much lower than what is prescribed in the guidelines (because these test substances were acids). The pH was so low it may have affected the survivability of the fish. These doses will therefore not be regarded further in the risk assessment. As 50 % mortality was not obtained in the relevant tests, the EC50-values are expressed as greater than the highest concentration with an acceptable pH.

The tests indicate that all three metabolites have adverse effects on the survival of fish. Both PSA and OMSA are much less toxic than the mother substance. However, the disulphide is probably almost as acutely toxic to fish as pyrithione, with NOECs of 11–520 µg/l (nominal concentrations), and EC50 values of 30–1100 µg/l. For instance, in one study (Doc III A7.4.1.1/16, 1995), fathead minnows exposed to water containing pyrithione disulfide (renewed every 24 h) showed a 96-hour LC_{50} of 30 µg/l with a 95 % confidence interval of 25 to 40 µg/l. The estimated 96-hour NOEC was 11 µg/l.

(A few test results were interpreted differently in the Reach registration dossier. The following studies have received a different

LC50 value in the Reach registration: DOCA7.4.1.1/11: LC50 92.3 mg/l, DOCA7.4.1.1/12: LC50 57.1 mg/l, A7.4.1.1/17: LC50 58.8 mg/l, A7.4.1.1/18: LC50 68.5 mg/l)

A4.2.3.1.2 Acute toxicity to invertebrates

Two tests, for acute toxicity to invertebrates, with sodium pyrithione are available. Both studies show a LC50 < 1 mg/l. The studies are included here for information as the Klimisch reliability score of the tests is only considered to be 3. Based on the available information the most sensitive species is a fish. (Studies with NaPT metabolites are presented in Tables A4.2.3.1.2-01 to 03.)

Doc III A7.4.1.2/01, 1994 RI = 3
The toxicity of acute exposure of the sodium pyrithione on *Daphnia magna* was evaluated according to OECD 402 and 92/69/EEC, C.2. Twenty *Daphnia* each were exposed to 0; 0.050; 0.20; 0.80; 3.2; 13; and 51 mg product per litre (of which 40% was sodium pyrithione). Light was on for 16 h followed by 8 h dark, with a 15 min transition period. The 48-h EC50 was 0.15 mg/l (nominal NaPT), the 48-h EC0 was 0.02 µg/l (nominal NaPT). Only nominal concentrations can be used because the validity criteria were not fulfilled. It was not demonstrated that the actual concentration was above 80 % of the nominal. The authors thought it was, because they trusted their chemical analysis method (UV-absorption without any chromatographic separation). The SE CA do not trust the method for chemical analysis.

Doc III A7.4.1.2/02/Anonymous, 1976 RI = 3
The toxicity of acute exposure of the sodium pyrithione on *Daphnia magna* was tested in an early version of the test. Lake water was used as diluent water. The results are very poorly documented. LC0 was 11.5 µg/l, LC50 was 22.0 µg/l, and LC100 was > 37 µg/l. The 48 hour LC50 for sodium pyrithione to *D. magna* with 95% confidence limits was 22.0 (17.9–27.1) µg/l. This value is based upon nominal concentrations of 100% active sodium pyrithione.

REACH registration dossier, JS member, Opt-out, 2002
An immobilization study performed according to OECD guideline 202 with *Daphnia magna* was included in the Reach-registration dossier. The nominal test concentrations in the study were: 0.1, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6 and 10 mg/L. A couple of the measured values, 0.1 mg/L at 0 hours and 0.32 mg/L at 48 hours, ended up outside the allowed range (80 – 120 %). These values are explained by problems with the analytical method and difficulty to determine low concentrations of the test substance in a complex biological system according to the registrant. All other measured test concentrations were within the allowed range. The full study report is not available to the DS, but the Reach-registrant has given the study a reliability of 1. The EC50 of 0.6 mg NaPT/l based on nominal values, is not the most conservative among the short-term toxicity results for aquatic organisms.

Summary

In conclusion, the available data indicate that sodium pyrithione has a high toxicity towards invertebrates with EC50 <1 mg/l.

Metabolites

Table A4.2.3.1.2-01 Acute toxicity of pyridine-N-oxide-2-sulfonic acid ("OMSoA"/"OMSA") to invertebrates

Guideline / Test method	Species	Endpoint / Type of test	Exposure design	duration	Results [mg/l] NOEC	LC50	EC50	Reference
US EPA-72-2	*Daphnia magna*	Immobility and mortality	Flow-through	48 h	127		>127	Doc III A7.4.1.2/11 Year: 1994 RI = 2
US EPA – 72-3(b)	*Mysidopsis bahia*	Mortality	Static	96 h	32.2	71.3		Doc III A7.4.1.2/14 Year: 1994 RI = 2
US EPA	*Crassostrea virginica*	Shell growth	Flow-through	96 h	35.6		99.2	Doc III A7.4.1.2/17 Year: 1994 RI = 2

Table A4.2.3.1.2-02 Acute toxicity of pyridine sulphonic acid ("PSA" or "PSoA") to invertebrates

Guideline / Test method	Species	Endpoint / Type of test	Exposure design	duration	Results [mg/l] NOEC	LC50	EC50	Reference
US EPA-72-2	*Daphnia magna*	Immobility and mortality	Flow-through	48 h	122		>122	Doc III A7.4.1.2/12 Year: 1994 RI = 2
US EPA-72-3(b)	*Mysidopsis bahia*	Mortality	Flow-through	96 h	51.9	71.6		Doc III A7.4.1.2/15 Year: 1994 RI = 2
US EPA	*Crassostrea virginica*	Shell growth	Flow-through	96 h	51.1	85.6		Doc III A7.4.1.2/18 Year: 1994 RI = 2

Table A4.2.3.1.2-03 Acute toxicity of 2,2'-(pyridyl-N-oxide) disulphide ("OMDS") to invertebrates

Guideline / Test method	Species	Endpoint / Type of test	Exposure design	duration	Results [mg/l] NOEC	LC50	EC50	Reference
US EPA-72-2	*Daphnia magna*	Immobility and mortality	Static renewal (24 h)	48 h	0.006		0.013	Doc III A7.4.1.2/10 Year: 1995 RI = 3 due to nominal concentrations, but acceptable for classification purpose.
US EPA-72-3(b)	*Mysidopsis bahia*	Mortality	Static renewal (24 h)	96 h	0.004	0.0064		Doc III A7.4.1.2/13 Year: 1995 RI = 3 due to nominal concentrations, but acceptable for classification purpose.
US EPA-72-3(c)	Eastern oyster *Crassostrea virginica*	Shell growth	Static renewal (24 h)	96 h	0.11		0.16	Doc III A7.4.1.2/16 Year: 1995 RI = 3 due to nominal concentrations, but acceptable for classification purpose.

Metabolites: Aquatic toxicity tests with invertebrates and pyrithione metabolites.

Acute toxicity tests for organic metabolites were submitted. These were performed with the metabolites PSA, OMSA and pyrithione disulphide (OMDS), using *Daphnia magna*, *Mysidopsis bahia* and *Crassostrea virginica* as test species. The tests were all guideline studies.

All three metabolites affected the Mysid and the Eastern oyster adversely, whereas pyrithione disulphide had the most adverse effect on *Daphnia magna.* The ecotoxicity of OMDS is probably in comparison with pyrithiones. For instance, exposure of mysids to statically renewed solutions (every 24 h) of omadine disulfide resulted in a 96 hour LC50 of 6.4 µg/l (nominal concentration) with a 95 % confidence interval of 5.7 to 7.4 µg/l (Doc III A7.4.1.2/13, 1995). The estimated 96 hour NOEC was 4.0 µg/l (nominal concentration), which was the lowest concentration tested.

A4.2.3.1.3 Acute toxicity to algae

DOCIII A7.4.1.3/01, 1994, RI = 2

A toxicity study with the freshwater algae *Selenastrum capricornutum* and sodium pyrithione has been submitted for the substance evaluation under BPR (EU) 528/2012. The nominal test substance exposure concentrations used in this study were 0.025, 0.050, 0.10, 0.20, 0.40, 0.80, 1.6 and 3.2 mg per litre together with a control. These were equivalent to 0.010, 0.020, 0.040, 0.080, 0.16, 0.32, 0.64 and 1.3 mg/1 of the active ingredient. After 48 h a LC50 of 460 µg/l based on growth rate and a 48 h LC50 of 230 µg/l based in biomass were obtained. The LC50s reported are calculated by multiplying the nominal values with 0.402 (the sodium pyrithione content of the product). The study is assigned a reliability of 2 as it is a well reported guideline study while the chemical analysis, however, is considered unspecific. No recovery efficiency of the method is reported. Furthermore, the purity of NaPT is not reported. The study results are acceptable for the purpose of classification.

REACH registration dossier, JS member, Opt-out, 2002
A growth inhibition test with the algae *Desmodesmus subspicatus* is included in the Reach registration dossier. The test concentrations used in the study were: 0.0625, 0.125, 0.25, 1.0 and 0.5 mg/l. The measured values were not within the range of 80 - 120 % of nominal values. At 72 hours the measured concentrations showed a steep decline to only 20 – 30 % of the nominal values. Therefore, the registrant based the results on time-weighted-average of mean measured concentrations. The full study report is not available to the DS and it is not possible to determine whether the validity criteria has been fulfilled based on the information provided. The Reach-registrant has given the study a reliability of 1.

The EC50 results for short-term toxicity obtained from the two algae studies are not the most conservative EC50 values among the ecotoxicity results available for NaPT. The most sensitive species is a fish with regards to short-term effects. The NOEC values derived from the two algae studies are discussed in section "Chronic/long-term toxicity (freshwater)".

Metabolites

Table A4.2.3.1.3-01 Growth inhibition effects of pyridine-N-oxide-2-sulfonic acid ("OMSA"/"OMSoA") on algae

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results (mg/L)		Reference
			design	duration	NOEC	EC_{50}	
US EPA-122-2	Fresh water algae *Selenastrum capricornutum*	Growth inhibition	Static	120 hours	2.17	>16.75	Doc III A7.4.1.3/11, Year: 1994 RI = 2

Table A4.2.3.1.3-02 Growth inhibition effects of pyridine sulphonic acid ("PSA") on algae

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results (mg/L)		Reference
			design	duration	NOEC	EC_{50}	
US EPA-122-2	Fresh water algae *Selenastrum capricornutum*	Growth inhibition	Static	120 hours	5.46	>32	Doc III A7.4.1.3/12, Year: 1994 RI = 2

Table 4.2.3.1.3-03 Growth inhibition effects of 2,2'-(pyridyl-N-oxide) disulphide ("OMDS") on algae

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results (mg/L)		Reference
			design	duration	NOEC	EC_{50}	
US EPA-122-2	Fresh water algae *Selenastrum capricornutum*	Growth inhibition	Static	120 hours	0.080 nominal	0.140 nominal	Doc III A7.4.1.3/10, Year : 1995 RI = 3 due to nominal concentrations, but acceptable for classification purpose

Metabolites: Aquatic toxicity tests with algae and pyrithione metabolites.

Acute toxicity tests for organic metabolites were submitted. The effect of metabolites PSA, OMSA and pyrithione disulphide (OMDS) was tested, using the freshwater alga *Selenastrum capricornutum* as test organism.

In the tests performed with OMSA and PSA, the pH was much lower than what is prescribed in the guidelines. The low pH may have affected the growth of the algae. The affected doses will therefore not be regarded further in the risk assessment. As 50 % inhibition was not obtained in the relevant tests, the EC_{50}-values are expressed as greater than the highest concentration with an acceptable pH.

All three metabolites were shown to have an adverse effect on the growth of *Selenastrum capricornutum*, and the results for OMDS indicate an acute toxicity towards algae.

A.4.2.3.1.4 Chronic/long-term toxicity (freshwater)

DOCIII A7.4.1.3/01, 1994 and REACH registration dossier, JS member, Opt-out, 2002
As shown in Summary Table A4.2.3.1.3 and discussed in section "Acute toxicity to algae" there are two available growth inhibition studies with algae. The NOEC obtained from algae growth inhibition tests are considered acceptable for assessment of long-term aquatic toxicity for classification purposes. There are some concerns regarding the precision of analytical method for both of the studies and due to limited reporting for the study included in the Reach registration dossier there is not enough information to evaluate the validation criteria. However, the results from the algae studies are the only long-term toxicity values available for NaPT and nominal values can shed some light on the degree of toxicity of NaPT to algae (even if the actual values probably would be somewhat lower). A comparison of the two NOEC values from each respective study show that the NOEC-values are in the same order of magnitude, which thereby gives some support to the results. For the purpose of classification both NOECs based on growth rate, 0.08 mg/l (nominal) and 0.033 (measured) point towards the same classification for chronic aquatic toxicity, which is Category Chronic 2.

A4.2.3.2 Sediment compartment
No studies investigating the toxicity for sediment dwelling organisms are available for sodium pyrithione.

A4.2.3.3 Marine compartment
No studies investigating the toxicity for marine organisms are available for sodium pyrithione.

A4.2.3.4 Sea sediment compartment
No studies investigating the toxicity for marine sediment dwelling organisms are available for sodium pyrithione.

A.4.2.4. Terrestrial compartment

Not applicable for CLH report

A.4.2.5. Groundwater

Not applicable for CLH report.

A.4.2.6. Birds and mammals

Not applicable for CLH report.

A.4.2.7. Primary and secondary poisoning

Not applicable for CLH report.

A.4.3. Endocrine disruption

Not applicable for CLH report.

A.4.4. Derivation of PNECs

Not applicable for CLH report.

A.4.5. Overall summary of acute and chronic aquatic toxicity data and Comparison with the CLP criteria

A.4.5.1. Short-term (acute) aquatic hazard

The most conservative results, for short-term acute aquatic hazards and each trophic level, are summaries in the Table A.106. The results for the most stabile metabolite PSA, presented previously in the present report, show lower toxicity than the parent compound NaPT. Therefore, the results considered reliable for PSA are not presented in the summary table again.

Table A.106 Summary of the most conservative results on acute/ short-term aquatic toxicity relevant for acute classification.

Method	Sepecies	Test material	Results LC50	Remarks (RI set by Reach	Reference

			(mg/l)	registrant are in brackets)	
Fish					
OECD 203 GLP Method C.1 of Commission Regulation (EC) No 440/2008. Flow-through	Freshwater *Danio rerio*	NaPT	LC50 = 0.0077 (measured)	RI = 2 **(Key)**	BPR Art. 95 dossier Year: 2015, (unpublished)
Invertebrates					
OECD 202 GLP	Freshwater *Daphnia magna*	NaPT	0.150	Nominal RI = 3 (RI = 1)	Doc III A7.4.1.2/01/ Smyth et al., Year: 1994
Algae					
OECD 201 GLP	Freshwater algae *Desmodesmus subspicatus*	NaPT	0.22r	Measured (RI = 1) The DS does not have the full study report.	REACH registration dossier, JS member, Opt-out Year: 2002

r = inhibition based on growth rate

A.4.5.2. Long-term chronic aquatic hazard

The available results for long-term toxic effects to aquatic organisms are summarised in Table A.107. The studies are performed with two different algae species and both studies are performed with NaPT as a test substance.

Table A.107 Summary of the available results on chronic/long-term aquatic toxicity relevant for chronic classification.

Method	**Species**	**Test material**	**Results NOEC (mg/l)**	**Remarks (RI set by Reach registrant are in brackets)**	**Reference**
Algae					
OECD 201 GLP	Freshwater algae *Selenastrum*	NaPT	0.080r	Nominal RI = 2	Doc III A7.4.1.3/01

	capricornutum			(RI = 1)	Year: 1994
OECD 201 GLP	Freshwater algae *Desmodesmus subspicatus*	NaPT	0.033r	Measured (RI = 1) The DS does not have the full study report.	REACH registration dossier, JS member, Opt-out Year: 2002

r = inhibition based on growth rate

A.4.5.3. Conclusion on classification and labelling for environmental hazards and comparison with the CLP criteria

Acute aquatic hazard

The most sensitive species in the aquatic environment, based on the available information, is a fish. From the key fish study for acute toxicity with *Danio rerio* the lowest value was obtained: LC50 = 7.7 µg/l. As the 96 h LC50 value for fish is ≤ 1 mg/l the substance can be classified as Category Acute 1 (aquatic environment).

Long-term aquatic hazard

According to the classification strategy in CLP for long-term hazards in the aquatic environment the following should be assessed when there is only adequate chronic toxicity data for one or two trophic levels:

1) compare the chronic toxicity data available to the criteria given in the Table 4.1.0 (b)(i) or 4.1.0 (b)(ii) depending on information on rapid degradation
and
2) compare the available adequate acute toxicity data for the other trophic levels, to the criteria given in Table 4.1.0 (b)(iii)

The most stringent outcome should be used for classification.

The strategy with regards to NaPT is discussed below.

Regarding the available chronic toxicity data: There are two available 72 hour growth inhibition studies with algae from which both EC50 and NOECs were obtained. The NOEC obtained from 72 h algae growth inhibition tests are considered acceptable for assessment of long-term aquatic toxicity for classification purposes. There are some concerns regarding the precision of analytical

method for both of the studies and due to limited reporting for the study included in the Reach registration dossier there is not enough information to evaluate the validation criteria. However, the results from the algae studies are the only long-term toxicity values available for NaPT and nominal values can shed some light on the degree of toxicity of NaPT to algae, even if the actual values probably would be somewhat lower. A comparison of the two NOEC values from each respective study show that the NOEC-values are in the same order of magnitude, which thereby gives some support to the results. For the purpose of classification both NOECs based on growth rate, 0.08 mg/l (nominal) and 0.033 mg/l (measured) point towards the same classification for chronic aquatic toxicity, which is Category Chronic 2.

Regarding the application of EC50 values as a substitute for long-term data for the purpose of chronic classification: Sodium pyrithione and the most stable of the degradation products, PSA, are both considered readily degradable. Due to the degradability and a low log K_{OW} no bioaccumulation is expected either. According to the criteria in the Table 4.1.0 (b)(iii) this information (readily degradable and low log Kow) means that this approach will lead to no classification for chronic toxicity for the aquatic environment.

In conclusion, as the most stringent approach should be adopted, the DS propose Category Chronic 2 for NaPT with regards to long-term effects in the aquatic environment.

Conclusion

The DS propose a classification for sodium pyrithione as follows:
Category Acute 1, M-factor = 100 (0.001 mg/l < LC50 ≤ 0.01 mg/l).
Category Chronic 2 (0.01 mg/l < NOEC ≤ 0.1 mg/l).

A.5. Assessment of additional hazards

A.5.1. Hazardous to the ozone layer

Hazard class not assessed in this dossier

A.6. Additional Labelling

Not relevant.

A.7. Assessment of exclusion criteria, substitution criteria and POP

Not applicable for the CLH report.

B. Exposure assessment and effects of the active substance in the biocidal product(s)

Not applicable for the CLH report.

C. Risk characterisation of the biocidal product(s)

Not applicable for the CLH report.

D. Appendices

APPENDIX I: LIST OF ENDPOINTS

Not applicable for the CLH report.

APPENDIX II: HUMAN EXPOSURE CALCULATIONS

Not applicable for the CLH report.

APPENDIX III: ENVIRONMENTAL EMISSION (AND EXPOSURE) CALCULATIONS

Not applicable for the CLH report.

APPENDIX IV: LIST OF TERMS AND ABBREVIATIONS

DS	Dossier Submitter
ESPTF	European Sodium Pyrithione Task Force
NaPT	Sodium pyrithione
PSA	Pyridine sulphonic acid

APPENDIX V: OVERALL REFERENCE LIST (INCLUDING DATA OWNER AND CONFIDENTIALITY CLAIM)

All the references are included under the respective sections in the main part of the CLH report.

APPENDIX VI: CONFIDENTIAL INFORMATION

None.

APPENDIX VII: STUDY SUMMARIES (IF RELEVANT FOR THE CLH PROPOSAL)

The study summaries from draft NaPT CAR Doc IIIA referred to in this report are provided as confidential appendices to ECHA.