CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

1,4-dimethylnaphthalene

EC Number: 209-335-9

CAS Number: 571-58-4

Index Number: -

Contact details for dossier submitter:

Bureau REACH
National Institute for Public Health and the Environment (RIVM)
The Netherlands
bureau-reach@rivm.nl

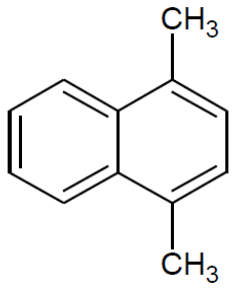
Version number: 2.0 **Date: December 2018**

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

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

Name(s) in the IUPAC nomenclature or other international chemical name(s)	1,4-dimethylnaphthalene
Other names (usual name, trade name, abbreviation)	1,4-DMN
ISO common name (if available and appropriate)	Not available.
EC number (if available and appropriate)	209-335-9
EC name (if available and appropriate)	1,4-dimethylnaphthalene
CAS number (if available)	571-58-4
Other identity code (if available)	CIPAC: 822
Molecular formula	$C_{12}H_{12}$
Structural formula	
SMILES notation (if available)	Not available.
Molecular weight or molecular weight range	156.23
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	No stereoisomers.
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not relevant.
Degree of purity (%) (if relevant for the entry in Annex VI)	Minimum purity 98%

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
1,4-dimethylnaphthalene	**98%**	**None**	**Asp. Tox. 1, Eye Irrit. 2,**

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
CAS: 571-58-4			Aquatic Acute 1, Aquatic Chronic 1

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

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Not relevant impurities.				

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

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
No additives.					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: Proposed classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal		1,4-dimethylnaphthalene	209-335-9	571-58-4	Asp. Tox. 1 Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 2	H304 H319 H400 H411	GHS07 GHS08 GHS09 Dgr	H304 H319 H410	-	M = 1	
Resulting Annex VI entry if agreed by RAC and COM		1,4-dimethylnaphthalene	209-335-9	571-58-4	Asp. Tox. 1 Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 2	H304 H319 H400 H411	GHS07 GHS08 GHS09 Dgr	H304 H319 H410	-	M = 1	

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class needs not to be applied based on chemical structure of the substance.	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	Data conclusive but not sufficient for classification	Yes
Flammable solids	Hazard class not applicable	No
Self-reactive substances	Hazard class needs not to be applied based on chemical structure of the substance	Yes
Pyrophoric liquids	Data conclusive but not sufficient for classification	Yes
Pyrophoric solids	Hazard class not applicable	No
Self-heating substances	Hazard class not applicable	No
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	Yes
Oxidising liquids	Data conclusive but not sufficient for classification	Yes
Oxidising solids	Hazard class not applicable	No
Organic peroxides	Hazard class not applicable	No
Corrosive to metals	Data lacking	No
Acute toxicity via oral route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Data conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	Harmonised classification proposed	Yes
Respiratory sensitisation	Data lacking	No
Skin sensitisation	Data conclusive but not sufficient for classification	Yes
Germ cell mutagenicity	Data conclusive but not sufficient for classification	Yes
Carcinogenicity	Data conclusive but not sufficient for classification	Yes
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	Data conclusive but not sufficient for classification	Yes
Aspiration hazard	Harmonised classification proposed	Yes
Hazardous to the aquatic environment	Harmonised classification proposed	Yes

Hazard class	Reason for no classification	Within the scope of public consultation
Hazardous to the ozone layer	Data lacking	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

1,4-dimethylnaphthalene has not been previously classified by RAC or TC C&L.

1,4-dimethylnaphthalene is not registered under REACH (October 2017) and has not been notified in the C&L inventory. Eight other dimethylnaphthalene substances have been notified. Dimethylnaphthalene (CAS 28804-88-8) and 1,5-dimethylnaphthalene are both self-classified as eye irrit 2, skin irrit 2 and as STOT SE 3 (H335).

According to the data presented in the DAR (October 2012), the classification of 1,4-dimethylnaphthalene is: Eye irritant Cat 2, Aquatic Acute 1 and Aquatic Chronic 1.

The conclusions on the peer review risk assessment of 1,4-dimethylnaphthalene was published as EFSA conclusion (EFSA Journal 2013;11(10):3229). The classification was unchanged. The DAR can be requested via: http://dar.efsa.europa.eu/dar-web/provision. EFSAs peer review is available via the EFSA website (http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3229/pdf).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

1,4-dimethylnaphthalene is an active substance in the meaning of Regulation EC 1107/2009 and therefore no justification is required.

5 IDENTIFIED USES

1,4-dimethylnaphthalene is intended for use as dormancy enhancer in potatoes during storage. The product is applied by hot or cold fogging.

6 DATA SOURCES

This reports has been prepared based on the data on 1,4-dimethylnaphthalene that was submitted for the Annex 1 inclusion and the evaluation in the DAR.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Clear liquid at 21°C	IIA 2.1/02 Doc ID 4373-93-0226-AS	Measured
Melting/freezing point	1°C	IIA 2.3/01, Doc ID 4373-93-0249-AS	Measured
Boiling point	264 °C at 744 mm Hg (=9.91x10^4 Pa)	IIA 2.1/02 Doc ID 4373-93-0226-AS	Measured
Relative density	1.014 at 25 °C	IIA 2.1/02 Doc ID 4373-93-0226-AS	Measured
Vapour pressure	2.50 ± 0.096 Pa at 24.8 ± 0.66 °C (n=7; 1s) 4.85 ± 1.279 Pa at 34.9 ±	IIA 2.3/01, Doc ID 4373-93-0249-AS	Measured

Property	Value	Reference	Comment (e.g. measured or estimated)
	0.07 °C (n=6; 1s) 11.7 ± 1.319 Pa at 44.9 ± 0.09 °C (n=6; 1s)		
Surface tension	36.88 dyne cm^{-1} at 25 °C (36.88 mN/m)	IIA 2.14/01	Non-GLP public literature study. No information on test method is available. Study not acceptable. However, considering the molecule structure of 1,4-DMN (no hydrophilic groups), surface active properties are not expected.
Water solubility	5.1 ± 0.16 mg L^{-1} at 25 ± 1 °C	IIA 2.6/01, Docu ID 4373-93-0250-AS-001	Measured
Partition coefficient n-octanol/water	log P 4.37 ± 0.012 at 22.5 ± 0.5 °C (1s).	IIA 2.8/01	Measured. non-GLP public literature study
Flash point	122 °C at 760 mm Hg (= $1.01x10^5$ Pa)	IIA 2.1/02 Doc ID 4373-93-0226-AS	Measured.
Flammability	No data.		
Explosive properties	Not sensitive to impact and Expert statement	IIA 2.1/02 Doc ID 4373-93-0226-AS IIA 2.3/02	Measured. There are no chemical groups present that indicate explosive properties.
Self-ignition temperature	Expert statement	Document N (applicant)	1,4-dimethylnaphthalene is not considered autoflammable.
Oxidising properties	Expert statement	IIA 2.3/02	There are no chemical groups in 1,4-dimethylnaphthalen that indicate oxidising properties
Granulometry	No data.		-
Stability in organic solvents and identity of relevant degradation products	No data.		-
Dissociation constant	Expert statement	Document N (applicant)	Based on the molecular structure, 1,4-dimethylnaphthalene will not dissociate in water.
Viscosity	Mean viscosity was 6 mPa s at 12 rounds per minute and 6 mPa s at 30 rounds per minute at 25 °C. The kinematic viscosity is 6 mPa.s / 1.014 = 5.9 mm^2/s.	IIA 2.1/02 Doc ID 4373-93-0226-AS	Measured.

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Table 8: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
FIFRA § 63-16 Impact apparatus	Not sensitive to impact at 25°C	-	IIA 2.1/02 Doc ID 4373-93-0226-AS

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

A study (IIA 2.1/02) was conducted to determine the impact explodability of 1,4-DMN batch H5510 at 25°C using the Bureau of Explosives impact apparatus. The minimum explosive drop height was 31 1/4 inches (maximum drop height). Three replicates were carried out. No explosive behaviour was observed.

8.1.2 Comparison with the CLP criteria

No explosive behaviour was observed in an impact explodability study. In addition, there are no chemical group in 1,4-dimethylnaphthalene that indicate explosive properties as given in section 2.1.4.2 of the CLP guidance. The impurities are largely comparable to the active substance and also do not include groups that may induce explosive behaviour in the sense of EC A14. Therefore, no classification is proposed.

8.1.3 Conclusion on classification and labelling for explosive properties

No classification is proposed.

8.2 Flammable gases (including chemically unstable gases)

Hazard class not applicable. 1,4-dimethylnaphthalene is not a gas.

8.2.1 Short summary and overall relevance of the provided information on flammable gases (including chemically unstable gases)

Not relevant.

8.2.2 Comparison with the CLP criteria

Hazard class not applicable.

8.2.3 Conclusion on classification and labelling for flammable gases

Hazard class not applicable (1,4-dimethylnaphthalene is not a gas).

8.3 Oxidising gases

Hazard class not applicable. 1,4-dimethylnaphthalene is not a gas.

8.3.1 Short summary and overall relevance of the provided information on oxidising gases

Not relevant.

8.3.2 Comparison with the CLP criteria

Hazard class not applicable.

8.3.3 Conclusion on classification and labelling for oxidising gases

Hazard class not applicable. 1,4-dimethylnaphthalene is not a gas.

8.4 Gases under pressure

Hazard class not applicable (1,4-dimethylnaphthalene is not a gas).

8.4.1 Short summary and overall relevance of the provided information on gases under pressure

Not relevant.

8.4.2 Comparison with the CLP criteria

Hazard class not applicable.

8.4.3 Conclusion on classification and labelling for gases under pressure

Hazard class not applicable (1,4-dimethylnaphthalene is not a gas).

8.5 Flammable liquids

Table 9: Summary table of studies on flammable liquids

Method	Results	Remarks	Reference
FIFRA § 63-15 (ASTM D 93-90, CIPAC MT12.3) Pensky-Martens apparatus equivalent to EEC A9	Flashpoint: 122 °C at 760 mm Hg (= 1.01×10^5 Pa)	-	IIA 2.1/02 Doc ID 4373-93-0226-AS
FIFRA § 63-6 (ASTM D 1120-89, ebulliometric method) equivalent to OECD TG103 and EEC A2.	Boiling point: 264 °C at 744 mm Hg ($=9.91 \times 10^4$ Pa)	-	IIA 2.1/02 Doc ID 4373-93-0226-AS

8.5.1 Short summary and overall relevance of the provided information on flammable liquids

A study was conducted to determine the flammability of 1,4-DMN (batch H5510) using a test guideline equivalent to EEC A9 (IIA 2.1/02). The test was run in duplicate. The mean flash point corrected to a barometric pressure of 760 mm Hg was 122°C.

An experiment was conducted to determine the boiling point of 1,4-DMN (batch H5510) (IIA 2.1/02). The test was run in duplicate. The test was repeated with a standard material (ethylene glycol) of known boiling point. The atmospheric pressure was recorded in mm Hg at the conclusion of each test. The mean boiling point was 264°C at 744 mm Hg.

8.5.2 Comparison with the CLP criteria

According to the CLP Guidance a substance should be classified as a flammable liquid when:

Category 1: Flash point < 23 °C and initial boiling point ≤ 35 °C

Category 2: Flash point < 23 °C and initial boiling point > 35 °C

Category 3: Flash point ≥ 23 °C and initial boiling point ≤ 60 °C

Considering the flashpoint of 122°C and the boiling point of 264°C 1,4-dimethylnaphthalene does not need to be classified as a flammable liquid.

8.5.3 Conclusion on classification and labelling for flammable liquids

No classification is proposed.

8.6 Flammable solids

Hazard class not applicable (1,4-dimethylnaphthalene is not a solid).

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

Not relevant.

8.6.2 Comparison with the CLP criteria

Hazard class not applicable.

8.6.3 Conclusion on classification and labelling for flammable solids

Hazard class not applicable (1,4-dimethylnaphthalene is not a solid).

8.7 Self-reactive substances

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

No specific study available.

8.7.2 Comparison with the CLP criteria

No specific study has been submitted. However, 1,4-dimethylnaphthalene does not contain any chemical groups associated with explosive or self-reactive properties in accordance with Table 2.8.4.2 of the CLP guidance.

8.7.3 Conclusion on classification and labelling for self-reactive substances

No classification is proposed.

8.8 Pyrophoric liquids

No specific study was carried out.

8.8.1 Short summary and overall relevance of the provided information on pyrophoric liquids

No specific data derived in accordance with the recommended test method in CLP has been provided. However, 1,4-dimethylnaphthalene has been handled extensively in air within all studies available in the dossier and there are no reports of self-ignition.

8.8.2 Comparison with the CLP criteria

According to the additional classification considerations in CLP Annex I, 2.9.4, the classification procedure for pyrophoric liquids need not be applied when experience in manufacture or handling shows that the liquid does not ignite spontaneously on coming into contact with air at normal temperatures. 1,4-dimethylnaphthalene has been extensively handled in all studies (physicochemical studies, toxicity studies etc.) without reports of self-ignition. Therefore, no classification is proposed.

8.8.3 Conclusion on classification and labelling for pyrophoric liquids

No classification is proposed.

8.9 Pyrophoric solids

Hazard class not applicable (1,4-dimethylnaphthalene is not a solid).

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

Not relevant.

8.9.2 Comparison with the CLP criteria

Hazard class not applicable.

8.9.3 Conclusion on classification and labelling for pyrophoric solids

Hazard class not applicable (1,4-dimethylnaphthalene is not a solid).

8.10 Self-heating substances

Hazard class not applicable (1,4-dimethylnaphthalene is a liquid).

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

Not relevant

8.10.2 Comparison with the CLP criteria

Hazard class not applicable.

8.10.3 Conclusion on classification and labelling for self-heating substances

Hazard class not applicable (1,4-dimethylnaphthalene is a liquid).

8.11 Substances which in contact with water emit flammable gases

No data.

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

No specific data derived in accordance with the recommended test method in CLP has been provided. However, 1,4-dimethylnaphthalene has been handled in water within many of the studies available in the dossier and there are no reports of violent reaction and emission of gas

8.11.2 Comparison with the CLP criteria

Based on experience in handling of 1,4-dimethylnaphthalene, it is not a substance which in contact with water emit flammable gases.

8.11.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

No classification is proposed..

8.12 Oxidising liquids

No data.

8.12.1 Short summary and overall relevance of the provided information on oxidising liquids

No specific study was submitted.

8.12.2 Comparison with the CLP criteria

The CLP Guidance states that for organic substances or mixtures the classification procedure for this hazard class need not to be applied if:

a. the substance or mixture does not contain oxygen, fluorine or chlorine; or

b. the substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen.

As 1,4-dimethylnaphthalene does not contain these chemical groups no classification for oxidizing properties is required.

8.12.3 Conclusion on classification and labelling for oxidising liquids

No classification is proposed.

8.13 Oxidising solids

Hazard class not applicable. 1,4-dimethylnaphthalene is not a solid.

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

Not relevant.

8.13.2 Comparison with the CLP criteria

Hazard class not applicable.

8.13.3 Conclusion on classification and labelling for oxidising solids

Hazard class not applicable (1,4-dimethylnaphthalene is not a solid).

8.14 Organic peroxides

Hazard class not applicable (1,4-dimethylnaphthale is not a organic peroxide).

8.14.1 Short summary and overall relevance of the provided information on organic peroxides

Not relevant.

8.14.2 Comparison with the CLP criteria

Hazard class not applicable.

8.14.3 Conclusion on classification and labelling for organic peroxides

Hazard class not applicable (1,4-dimethylnaphthale is not a organic peroxide).

8.15 Corrosive to metals

No data has been provided that addresses this hazard class.

8.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

No data has been provided that addresses this hazard class..

8.15.2 Comparison with the CLP criteria

No data has been provided that addresses this property.

8.15.3 Conclusion on classification and labelling for corrosive to metals

No classification is proposed due to lack of data.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

The mammalian toxicity studies of 1,-4-dimethylnaphthalene were assessed in the Draft Assessment Report (October 2012) prepared in the context of the approval, under Reg. (EC) 1107/2009. All studies were carried out under GLP unless indicated otherwise. Other than the public literature studies all studies reported in this section were carried out in accordance with OECD guidelines. Minor deviations were noted in some cases but these did not affect the overall reliability of the studies. The deviations are included in the summaries where relevant. For the public literature studies the reliability of the studies were assessed using Klimisch Scores.

Table 10: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Public literature, non-GLP	Rapid excretion within 72 hours	Klimisch score 1	IIA 5.1/01

Method	Results	Remarks	Reference
1,4-dimethylnaphthalene (purity not reported), single dose i.p. at 28 mg/kg bw/day.	(57% via urine, 40.8% via faeces). No evidence of accumulation Metabolism via: oxygenation of alkyl side chain, ring hydroxylation yielding naphthols and binding of epoxide intermediates to glutathione leading to thionaphthols.		
Partially in accordance with OECD 417 Deviations: 3 instead of 4 animals, absorption and distribution not investigated. 1,4-dimethylnaphthalene, purity 98.28%, single oral dose 28.6 mg/kg	Rapid excretion essentially complete within 48 hours (71.6% via urine) Metabolism via oxygenation of alkyl side chains and ring hydroxylation yielding naphthols. No metabolites were found to confirm the 3rd pathway (binding of epoxide intermediates to glutathione leading to thionaphthols).	Study was carried out to confirm the results from the public literature study (IIA 5.1/01. The study is considered acceptable.	IIA 5.1/23, DocID 2263W-1
OECD 503 (metabolism in livestock) 1,4-dimethylnaphthalene, purity 97.7%, 7-day oral dose at 12.5 mg/kg bw/day	Rapid absorption (76%). No evidence of accumulation.	Study in goat was used to support absorption after oral exposure.	IIA 6.2/28

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

Some information is available on the oral **absorption** of 1,4-dimethylnaphthalene indicating an oral absorption of at least 72% (based on % found in urine). A study in the goat indicates that oral absorption in goats is at least 76%. Some public literature information was available for structurally similar naphthalenes (see Annex I for details). Oral absorption of 2-methylnaphthalene was at least 72% in guinea pigs. For 2-isopropylnaphthalene, oral absorption was at least 95% in rats, whereas in another rat study the oral absorption of monoisopropylnaphthalene was at least 78%. The oral absorption of 2,6-diisopropylnaphthalene was 85% in rats. On the basis of the results of the study with 1,4-dimethylnaphthalene in rats and goats and from the studies with 2-methylnaphthalene and mono- and di-isopropylnaphthalenes it can be assumed that the oral absorption of 1,4-dimethylnaphthalene will be high (>80%).

No information is available on the **distribution** of 1,4-dimethylnaphthalene after oral administration. After intraperitoneal administration, 1,4-dimethylnaphthalene and its metabolites were widely and rapidly distributed in rats. The highest concentrations were observed in adipose tissue, followed by liver, kidneys, spleen and adrenals. The skin was not examined. After 72 h tissue levels, including in adipose tissue, were low indicating that 1,4-dimethylnaphthalene or its metabolites do not accumulate. Similar patterns of distribution were found for the alkylated naphthalenes 1,2-dimethylnaphthalene and 1,6-dimethylnaphthalene after intraperitoneal administration (see Annex I for details). After oral administration of the structurally related 2-methylnaphthalene to guinea pigs, distribution was also rapid with the highest levels of parent and/or metabolites in the gallbladder, followed by the kidneys, liver and lung. Adipose tissue was not examined, but after intraperitoneal administration of 2-methylnaphthalene to mice this tissue revealed the highest concentration. 2-Methylnaphthalene is the

only compound for which both an oral and an intraperitoneal study was available, but the intraperitoneal study was too limited to conclude on route- or species-specific differences in distribution. Monoisopropylnaphthalenes and 2,6-diisopropylnaphthalene were also rapidly and widely distributed after single and repeated oral administration, with the highest levels of parent compound and/or metabolites in the adipose tissue, followed by the skin. Repeated administration of 2-isopropylnaphthalene to rats did not result in higher levels of parent compound in the various tissues.

Information is available on the **excretion** of 1,4-dimethylnaphthalene after oral administration: after a single oral dose of 1,4-dimethylnaphthalene, excretion is rapid and essentially complete after 48 hours, with urine being the primary route of excretion (71.6%). The amount found in faeces and cage wash after 48 hours was 27.5 and 5.6% respectively. The parent molecule was detected in trace amounts in urine. After intraperitoneal administration, 1,4-dimethylnaphthalene and its metabolites were excreted mainly via urine (56.5% within 72 h) but also via faeces (40.8% within 72 h, reflecting excretion via bile since the administration was intraperitoneally).

The metabolites found in rat urine after oral administration of 1,4-dimethylnaphthalene indicate that the **metabolism** of 1,4-dimethylnaphthalene proceeds via at least two different routes:

a) side chain oxidation resulting ultimately in the carboxylic acid 4-methyl-1-naphthoic acid (ca 12% of the dose),

b) ring hydroxylation resulting in 1,4-dimethylnaphthols.

The metabolites found in rat urine after intraperitoneal administration of 1,4-dimethylnaphthalene indicate that the metabolism of 1,4-dimethylnaphthalene proceeds via at least three different routes:

a) side chain oxidation resulting ultimately in the carboxylic acid 4-methyl-1-naphthoic acid (20% of the dose),

b) ring hydroxylation resulting in 1,4-dimethylnaphthols (ca 10% of the dose) via reactive epoxide with

c) subsequent binding of epoxide intermediates to glutathione via conjugation leading ultimately to 1,4-dimethyl-methylthionaphthalene (1.4% of the dose, indicating a minor pathway).

This 3rd pathway described for 1,4-dimethylnaphthalene, namely the binding of epoxide intermediates to glutathione leading to thionaphthols, excreted in urine as mercapturates involved the forming of 1,4-dimethyl-methylthionaphthalene; this thiomethyl derivate of 1,4-DMN was reported in small amounts after i.p administration, but is not detected after oral administration.

Metabolites of 1,4-dimethylnaphthalene are also excreted via bile and faeces, but biliary and faecal metabolites have not been identified. Compared to the structurally related alkylated naphthalenes 1,2-dimethylnaphthalene and 1,6-dimethylnaphthalene, the side chain oxidation route is more important and ring oxidation with subsequent glutathione conjugation route is less important for 1,4-dimethylnaphthalene.

For 2-methylnaphthalene, most metabolites identified in guinea pig urine resulted from side chain oxidation, but also metabolites that may involve ring epoxidation were found. All identified metabolites of mono- and diisopropylnaphthalenes in urine and bile of rats resulted from the side chain oxidation pathway.

After a single oral or intraperitoneal dose to mammals, alkylnaphthalenes demonstrate very similar profiles for absorption and excretion with rapid absorption and essentially complete excretion within 72

hours. All alkylnaphthalenes are extensively metabolised in rat, mouse and guinea pig. Rat and mouse urine contains metabolites formed by three different pathways (side chain oxidation, ring oxidation to naphthols and mercapturates via reactive epoxide with subsequent conjugation to glutathione). This similarity in mechanism supports the use of alkylnaphthalene ADME data in the assessment of 1,4-DMN.

In addition, the relative toxicity profiles for alkylnaphthalenes can be linked to the proportion of metabolism which occurs by side chain or ring oxidation. For 1,4- dimethylnaphthalene, the primary route of metabolism has been shown to be via side chain oxidation and therefore this compound is one of the least toxic alkylnaphthalenes. This provides further support for the use of data from the alkylnaphthalene chemical group as it provides a worst case assessment for the hazard to humans.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 11: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
FIFRA 152-10 (in line with OECD 401) Deviations: none	Rat, Sprague-Dawley (Crl:CD®BR) 5/sex/dose	1,4-dimethylnaphthalene (Batch H5510, purity 96.4%)	Single dose, gavage at 750, 1000, 1300, 1700, 2000, 2100, 2300 and 2500 mg/kg bw	2730 mg/kg bw	IIA 5.2/01, Doc ID L08456, study 6,7,8

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

Five rat/sex/dose were exposed to 1,4-dimethylnaphthale (purity 96.4%) to dose level of 750, 1000 and 2500 mg/kg bw in the first, 1300, 1700 and 2100 mg/kg bw in the second and 2000, 2300 and 2500 mg/kg bw in the third study (IIA 5.2/01). In a previous limit test at 5000 mg/kg bw al animals (10/10) died. The results from this study were included in the LD_{50} calculations.

Death occurred in group dose with 1700 mg/kg bw and higher (see Table 13). Signs of toxicity were observed in all dose groups. In the lowest dose group, signs were restricted to discolouration around the mouth and red and/or clear nasal discharge. In the other dose groups, clinical signs included hypoactivity, ataxia, coma, irritability, chromodacryorrhea, lacrimation, salivation, redness around the nose and/or eyes, wet/discoloured inguinal fur, coldness to the touch, hunched posture, diarrhoea, hair loss and discoloured paws. All surviving rats had recovered at 7 days after administration.

The calculated acute oral LD50 for 1,4-dimethylnaphthalene in male and female rats was 2730 mg/kg bw with a confidence interval of 2346-3178 mg/kg bw.

Table 12: Mortality in the acute oral toxicity study

	Part 1			Part 2			Part 3		
Dose group mg/kg bw	**750**	**1000**	**2500**	**1300**	**1700**	**2100**	**2000**	**2300**	**2500**

Males Females	0 0	0 0	5 5	0 0	0 1	0 1	1 0	1 0	2 3

10.1.2 Comparison with the CLP criteria

According to the Regulation EC No 1272/2008 a substance should be classified for acute oral toxicity when:

Category 1: ATE ≤ 5 mg/kg bw

Category 2: 5 < ATE ≤ 50 mg/kg bw

Category 3: 50 < ATE ≤ 300 mg/kg bw

Category 4: 300 < ATE ≤ 2000 mg/kg bw

Based on the LD_{50} value of 2730 mg/kg bw 1,4-dimethylnaphthalene does not have to classified for acute oral toxicity.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

No classification is proposed.

10.2 Acute toxicity - dermal route

Table 13: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
FIFRA 152-11 (in accordance with OECD 402) Deviations: none	Rabbit, New Zealand/White 5/sex	1,4-dimethylnaphthalene (batch H5510, purity 96.4%)	2000 mg/kg bw Single dose, 24h under occlusion	> 2000 mg/kg bw	IIA 5.2/02, Doc ID L08456, study 4

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

In an acute dermal toxicity study (IIA 5.2/02) the undiluted test substance was administered to rabbit for 24 hours after which the test substance was wiped off with a gauze pad moistened with saline. Rabbits were observed for 14 days after administration.

No mortality occurred throughout the study. Except for 1 rabbit, all animals gained weight during the study. Treatment-related signs of systemic toxicity were not observed. Signs of dermal irritation at the application site (oedema and erythema) were observed in all rabbits immediately following removal of the wrappings. All animals developed eschar formation within five days following unwrapping. In 4 animals, eschar formation persisted until the end of the 14 days observation period. The LD_{50} was > 2000 mg/kg bw.

10.2.2 Comparison with the CLP criteria

According to the Regulation EC No 1272/2008 a substance should be classified for acute dermal toxicity when:

Category 1: ATE ≤ 50 mg/kg bw

Category 2: 50 < ATE ≤ 200 mg/kg bw

Category 3: 200 < ATE ≤ 1000 mg/kg bw

Category 4: 1000 < ATE ≤ 2000 mg/kg bw

Based on the LD_{50} value of >2000 mg/kg bw 1,4-dimethylnaphthalene does not have to classified for acute dermal toxicity.

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

No classification is proposed.

10.3 Acute toxicity - inhalation route

Table 14: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, , form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** LC_{50}	**Reference**
FIFRA 152-12 (in line with OECD 403) Deviations: temperature outside of 22 ±2°C range (25-26°C)	Rat, Sprague-Dawley (Crl:CD®BR) 5/sex	1,4-dimethylnaphthalene (batch H5510, purity 96.4%) MMAD: 2.82 µm	5 mg/L (target conc); 4.16 mg/L (achieved conc) Single dose, whole body, 4h	> 4.16 mg/L	IIA 5.2/03, DocID L08456L001

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In an acute inhalation study (IIA 5.2/03) Sprague-Dawley rats 5 male and 5 female animals were exposed to 4.16 mg/L 1,4-dimethylnaphthalene (achieved concentration). The mean aerosol Mass Median Aerodynamic Diameter (MMAD) of the chamber atmosphere was 2.82 µm (SD 1.67). Rats were observed for 14 days after exposure.

One rat died within 24 hours after administration. Clinical signs were observed in all animals and included dyspnea, prostration, ptosis, hypoactivity, discolouration around the mouth and/or nose and wet inguinal fur. In addition, tremors and red nasal and ocular discharge were also observed. Except for one animal, which showed ptosis on day 5 and 6 following exposure, all of the surviving rats appeared normal 3 days following the exposure. The incidences of the clinical signs are shown in the table below

Observation	Incidence		Timepoint observed
	Males	Females	
Eye discharge –red	1	2	Day 1-2
Ptosis	1	3	Day 5-6
Nasal discharge – red	0	3	Day 1-2
Dyspnea	0	1	Day 0
Hypoactive	1	5	Day 0-1
Prostate	0	3	Day 0-1
Tremors	0	1	Day 1

Discoloration around mounth	2	5	Day 0-1
Discoloration around nose	5	5	Day 0-1
Wet inguinal fur	5	4	Day 0-1

The acute median lethal inhalation dose (LC50) for 1,4-dimethylnaphthalene in adult male and female rats is > 4.16 mg/L.

10.3.2 Comparison with the CLP criteria

According to the Regulation EC No 1272/2008 a substance should be classified for acute inhalation toxicity when:

Category 1: ATE ≤ 0.05 mg/L

Category 2: 0.05 < ATE ≤ 0.5 mg/L

Category 3: 0.5 < ATE ≤ 1.0 mg/L

Category 4: 1.0 < ATE ≤ 5.0 mg/L

The achieved dose in the acute inhalation study was below the limit of 5 mg/L. However, it is not expected that an inhalation study in which rats would be exposed to 1,4-dimethylnaphthalene at an actual dose of 5 mg/L would result in a markedly different toxic profile and in a different conclusion with respect to classification and labelling than the results from the current study at 4.16 mg/L. The LC50 was found to be > 4.16 mg/L. Therefore, it is concluded that 1,4-dimethylnaphthalene does not need to be classified for acute inhalation toxicity.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

No classification is proposed.

10.4 Skin corrosion/irritation

Table 15: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results** **-Observations and time point of onset** **-Mean scores/animal** **-Reversibility**	**Reference**
FIFRA 152-14 (in line with OECD 404) Deviations: none	Rabbit, New Zealand White, 3/sex	1,4-dimethylnaphthalane (batch H5510, purity 94.6%)	0.5 ml, 4h, semi-occluded	Erythema (grade 1-2) and oedema (grade 1-3) from 1 h after exposure Mean scores: Erythema: 1.67; 2; 2; 2; 2; 2 Oedema: 1; 0.33; 0.67; 0.33; 0.33; 0.67 Reversible by day 14.	IIA 5.2/04, DocID L08456-study 2
FIFRA 152-11 (in	Rabbit, New Zealand/White	1,4-dimethylnaphthalene	2000 mg/kg bw	> 2000 mg/kg bw Eschar formation was observed within 5	IIA 5.2/02,

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
accordance with OECD 402) Deviations: none	5/sex	(batch H5510, purity 96.4%)	Single dose, 24h under occlusion	days following unwrapping.	Doc ID L08456, study 4

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

In a skin irritation study (IIA 5.2/04) 0.5 ml of undiluted 1,4-dimethylnaphthalene (purity 96.4%) was applied to the backs of 3 male and 3 female New Zealand White rabbits under semi-occluded conditions. After 4 h the application sites were wiped with gauze and 0.9% saline to remove residual test substance. Dermal changes were graded according to Draize. The skin was examined up to 14 days after application. Eyrtheme (grade 1-2) and oedema (grade 1-3) was observed in all animals at 1 hour after application (see Table 16). The effects were fully reversible by day 14 of the study. The individual mean scores were 1.67, 2, 2, 2, 2 and 2 for erythema and 1; 0.33, 0.67, 0.33, 0.33 and 0.67 for oedema.

Table 16: Individual skin irritation scores up to 14d after application

	1 h	24 h	48 h	72 h	7d	14d
erythema	1/2/2/1/1/1*	2/2/2/2/2/2	1/2/2/2/2/2	2/2/2/2/2/2	0/0/0/2/2/2	0/0/0/0/0/0
oedema	3/2/1/2/2/1	2/1/2/1/1/1	0/0/0/0/0/0	1/0/0/0/0/1	0/0/0/0/0/0	0/0/0/0/0/0

*m/m/m/f/f/f

In an acute dermal toxicity study (IIA 5.2/02) the undiluted test substance was administered to rabbit for 24 hours after which the test substance was wiped off with a gauze pad moistened with saline. Rabbits were observed for 14 days after administration. Signs of dermal irritation at the application site (oedema and erythema) were observed in all rabbits immediately following removal of the wrappings. All animals developed eschar formation within five days following unwrapping. In 4 animals, eschar formation persisted until the end of the 14 days observation period.

10.4.2 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP) Table 3.2.2 a substance should be classified for skin irritation Category 2 in the case where:

(1) Mean value of ≥ 2,3 - ≤ 4,0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or

(2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or

(3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.

In an acute dermal toxicity study carried out in accordance with OECD Guideline 402 signs of dermal irritation were observed which persisted until the end of the 14 days observation period. The irreversibility could be considered sufficient for classification as irritating. However, in a dermal irritation study following OECD Guideline 404 the mean erythema and oedema scores were below 2.3 in all animals and considering that the effects were fully reversible by day 14 no classification for skin irritation is required. As the exposure period in the acute dermal toxicity test (24 hours) was much longer than in the acute irritation test (4 hours) and occlusion instead of semi-occlusion was applied, the results of the dermal irritation study are given a higher weight than the results of the acute dermal toxicity study. The criteria for classification as irritant are not fulfilled.

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

No classification is proposed.

10.5 Serious eye damage/eye irritation

Table 17: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
FIFRA 152-13 (in line with OECD 405) Deviations: none	Rabbit, New Zealand White 3/sex	1,4-dimethylnaphthalene (batch H551, purity 96.4%)	0.1 ml (undiluted), single instillation in conjunctival sac	Conjuctival redness and chemosis from 1 hour after exposure. Mean Score: Corneal opacity: 0 Iris: 0 Conj. Redness: 1.67; 1.33; 1; 1; 1.67; 2 Conj. Chemosis: 1; 2; 2; 2; 2; 3	IIA 5.2/05, Doc ID L08456-study 1

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

In a eye irritation study (IIA 5.2/05) 0.1 ml undiluted 1,4-dimethylnaphthalene (purity 94.6%) was applied to the right eye of 3 male and 3 female New-Zealand White rabbits. Ocular changes were graded according to Draize. The eyes were examined up to 21 days after instillation.

Two rabbits were vocal immediately after administration of the test substance. Circumocular alopecia was observed in 3 animals at 14 days and in 2 animals at 21 days after application. The individual eye irritation scores are reported in table 19. The mean scores were 0 for corneal opacity and iritis. For conjuctival redness the individual mean scores were 1.67, 1.33, 1, 1, 1.67 and 2. For conjunctival redness and chemosis the individual mean scores were 1, 2, 2, 2, 2, 3.

Table 18: Individual eye irritation scores up to 21d after instillation

	1 h	24 h	48 h	72 h	Day 7	Day 14	Day 21
Corneal opacity	0/0/0/0/0/0*	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0
Corneal area	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0
Iris	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0
Conj. redness	2/2/2/2/2/2	2/2/2/2/2/2	2/1/1/1/2/2	1/1/0/0/1/2	1/1/0/0/1/2	0/0/0/0/1/0	0/0/0/0/0/0
Conj. chemosis	1/2/3/2/1/2	1/2/2/2/2/3	1/2/2/2/2/3	1/2/2/2/2/3	1/1/1/1/1/3	0/0/0/0/1/2	0/0/0/0/0/0
Conj. discharge	0/0/0/0/0/0	0/0/0/0/0/2	0/0/0/0/1/2	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0	0/0/0/0/0/0

* m/m/m/f/f/f

10.5.2 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP) Table 3.3.2.1.2 a substance should be classified for Serious eye damage Category 1 or eye irritation Category 2 in the case where:

a. Classification for serious eye damage – Category 1 if:

i. at least in 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; and/or(ii) at least 4 out of 6 rabbits show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis

b. Classification for eye irritation – Category 2 if at least 4 out of 6 rabbits show a mean score per animal of:

i. ≥ 1 for corneal opacity and/or

ii. ≥ 1 for iritis and/or

iii. ≥ 2 conjunctival erythema (redness) and/or

iv. ≥ 2 conjunctival oedema (swelling) (chemosis)

and which fully reverses within an observation period of normally 21 days.

The mean scores for corneal opacity and iritis was 0. For conjunctival redness the individual mean scores were below the criteria of 2 except for in 1 animal (out of 6). For conjunctival oedema the individual mean scores were ≥2 in 5 out of 6 animals which fulfils the criteria for category 2. The effects observed were fully reversible at day 21 and therefore classification as eye irritant Category 2 is required.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Harmonised classification proposed (Eye irritation Category 2).

10.6 Respiratory sensitisation

No data available.

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

No data available.

10.6.2 Comparison with the CLP criteria

Not relevant.

10.6.3 Conclusion on classification and labelling for respiratory sensitisation

No classification proposed, data lacking.

10.7 Skin sensitisation

Table 19: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
OECD 429 Deviations: none	mice, CBA/J 5/females/dose	1,4-dimethylnaphthalene (batch 14D06B01-01, purity 98.4%)	0, 25, 50 and 100% topical induction	SI for 25, 50% and 100%: 2.1, 2.4, 2.8	IIA 5.2/07, Doc ID 495316

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

In a LLNA study (IIA 5.2/07) four groups of five female CBA/J mice were treated to the control (acetone/olive oil 4:1 v/v) or to the 1,4-dimethylnaphthalene (purity 98.4%) at 25, 50 or 100% w/w on three consecutive days by topical application on the ears. Three days after the last exposure, all animals were injected via the tail vein with ^{3}H-methyl thymidine and after five hours the draining (auricular) lymph nodes were excised and pooled for each animal. After precipitating the DNA of the lymph node cells, radioactivity measurements were performed. The activity was expressed as the number of Disintegrations Per Minute (DPM) and a stimulation index (SI) was subsequently calculated for each group.

Enlarged auricular lymph nodes were found in the groups dosed at 50 and 100%. Mean DPM/animal values for the experimental groups treated with test substance concentrations 25, 50 and 100% were 1031, 1167 and 1384 DPM respectively. The mean DPM/animal value for the vehicle control group was 488 DPM. The SI values calculated for the substance concentrations 25, 50 and 100% were 2.1, 2.4 and 2.8, respectively.

10.7.2 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP) substance should be classified for skin sensitisation when the results of a LLNA study show a SI above 3. As this was not the case for 1,4-dimethylnaphthalene no classification for skin sensitisation is needed.

10.7.3 Conclusion on classification and labelling for skin sensitisation

No classification is proposed.

10.8 Germ cell mutagenicity

Table 20: Summary table of mutagenicity/genotoxicity tests in vitro

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Ames test, FIFRA 84-2 (in line with OECD 471) Deviations: TA1538 was tested instead of TA 102 or *E. coli*	1,4-dimethylnaphthalene (batch H5510, purity 96.4%)	Test system: TA98, TA100, TA1535, TA1537, TA1538 Test concentrations: +S9: 0, 10, 50, 100, 250, 500 and 1000 µg/plate -S9: 0, 1, 5, 10, 25, 50 and 250 µg/plate Based on range finding study. Positive controls: 2-aminoanthracene (all strains +S9), 2-nitrofluorene (TA98, TA1538 –S9), sodium azide (TA100, TA1535 –S9) and ICR-191 (TA1537 –S9)	Cytotoxicity: ≥ 333 µg/plate in the presence of S9 and doses ≥ 33.3 µg/plate in the absence of S9 No treatment related increase in revertant colonies.	IIA 5.4/01 Doc ID 15683-0-401
Ames test OECD 471 Deviations: none	1,4-dimethylnaphthalene (batch 14D03M01-02, purity 98.4%)	Test system: TA98, TA100, TA1535, TA1537, TA102 Test concentrations: Exp 1: 0, 0.128, 0.64, 3.2, 16, 80, 400 and 2000 µg/plate) Exp 2: 0, 1.638, 4.096, 10.24, 25.6, 64, 160, 400 µg/plate) Positive controls were 2-nitrofluorene (TA98, -S9), sodium azide (TA100 and TA1535, -S9), 9-aminoacridine (TA1537, -S9), mytomycin C (TA102, -S9), benzo[a]pyrene (TA98, -S9) and 2-aminoanthracene (all strains, +S9).	Cytotoxicity: ≥ 400 µg/plate in the presence of S9 and doses ≥ 80 µg/plate in the absence of S9 No treatment related increase in revertant colonies.	IIA 5.4/02 Doc ID 2782/2-D6171

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Mammalian gene mutation OECD 476 Deviations: none	1,4-dimethylnaphthalene (batch 14D03M01-02, purity 98.4%)	Test system: L5178Y mouse lymphoma cells Test concentrations: +S9: 50, 75, 100, 150, 170, 200, 210 and 220 µg/ml -S9: 1, 5, 10, 20, 30, 35, 37.5, 40 µg/ml Positive controls: methylmethanesulfonate (- S9) and cyclophosphamide (+S9)	Cytotoxicity: RTG <20% from 40 µg/plate in absence of S9 and from 210 µg/plate in presence of S9 Dose-related increase in mutant frequency outside of historical control in the presence of S9, but not in the absence of metabolic activation.	IIA 5.4/03 Doc ID 424711
Unscheduled DNA synthesis FIFRA 84/2(3) (in line with OECD 482) Deviations: no statistical analysis was carried out.	1,4-dimethylnaphthalene (batch H5510, purity 96.4%)	Test system: rat liver primary cell cultures Test concentrations: 0.250 -10 µg/ml Positive control: 2-acetylaminofluorene	Cytotoxicity: 58.2% survival at 10 µg/ml Gene mutation: equivocal	IIA 5.4/04 Doc ID 15683-0-447

Table 21: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells in vivo

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
In vivo micronucleus FIFRA 84.2 (in line with OECD 474) Deviations:	1,4-dimethylnaphthalene (batch H5510, purity 96.4%)	Male and female CD-1 (ICR) mice, 5/sex/dose Dose levels: 0, 225, 450, 900 mg/kg bw/day, single dose Positive controls:	Slightly reduced PCE:NCE in females (statistically significant, but within HCD) No treatment related increase in micronucleated PCE.	IIA 5.4/05 and IIA 5.4/06 Doc ID 15683-0-455 and 7931-100

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
none		cyclophosphamide		
In vivo Unscheduled DNA synthesis OECD 486 Deviations: acclimatisation period of 2 days instead of 5.	1,4-dimethylnaphthalene batch no: 14D03M01-02 (range-finding) and 14D06B01-01 (main study); purity: 98.4-98.6%)	Rats, Sprague Dawley, males (4/group) Dose levels: 0, 500, 1000 mg/kg bw. Positive controls: 2-cetamidofluorene and dimethylnitrosamine	No increase in net grain count.	IIA 5.4/07 Doc ID 1000/31-D6172

10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

<u>*In vitro* data:</u>

In a bacterial reverse mutation assay (IIA 5.4/01) 1.4-dimethylnaphthalene (batch H5510, purity 96.4%) was tested ranging from 10-1000 µg/plate in the presence of S9 and from 1-250 µg/plate in the absence of S9 mix. Used doses were based on a range finding study with TA100 with doses up to 5 mg/plate, which resulted in cytotoxicity at doses ≥ 333 µg/plate in the presence of S9 and doses ≥ 33.3 µg/plate in the absence of S9 (Aroclor 1254). The testes strains used in the study were TA98, TA100, TA1535, TA1537 and TA1538. 2-aminoanthracene was used as positive control in the presence of S9 and 2-nitrofluorene (TA98, TA 1538), sodium azide (TA100, TA 1535) and ICR-191 (TA1537) were used as positive controls in the absence of S9.
No increase in the number of revertants per plate were observed for strains TA98, TA100, TA1535 and TA1537. For strain TA1538 there was a 2.7 fold increase in revertants at a concentration of 250 µg/plate in the presence of S9. Although this increase was within the 3-fold range which was used in the study report as criteria for a positive effect it was decided to repeat the test in strain TA1538 in the presence of S9 in two separate experiments. No increase in revertant colonies was observed in these repeat studies. In was therefore concluded that 1,4-dimethylnaphthalene does not induce gene mutations in *S. typhimurium.*

Table 22: Summary table of the bacterial reverse mutation assay in strain TA1538 with S9

Dose level (µg/plate)	TA1538 (exp. 1)	TA1538 (exp. 2)	TA1538 (exp. 3)
0	16	14	18
10	14	14	17
50	16	15	20
100	23	16	20
250	43	20	18
500	2	0	14
1000	0	0	5
Positive control	940	1123	905

A second bacterial reverse mutation assay (IIA 5.4/02) was carried in accordance with OECD 471. 1,4-dimethylnaphthalene (batch no: 14D03M01-02; purity: 98.4%) was assasayed for mutation in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium*, both in the absence and in the presence of metabolic activation by an Aroclor 1254-induced rat liver post-mitochondrial fraction (S-9), in two separate experiments. Concentrations used were based on a range finding study with TA100. Appropriate positive controls were included.

In experiment 1, clear evidence of toxicity occurred in all strains at 400 µg/plate and above, in the absence and in the presence of S9, and also at 80 µg/plate in most strains in the absence of S9 and strain TA1535 in the presence of S9. In experiment 2, the dose range was narrowed and evidence of toxicity was observed in all strains at 64 µg/plate and above in the absence of S9 and 160 µg/plate and above in the presence of S9. 1,4-dimethylnaphthalene did not induce a biologically significant increase in revertant colonies. The positive controls induced the expected increases in revertant colonies in all strains. It was concluded that 1,4-dimethylnaphthale does not induce gene mutations in *S. typhimurium.*

A mammalian gene mutation study (IIA 5.4/03) evaluated the effect of 1,4-dimethylnaphthalene (batch no: 14D03M01-02; purity: 98.8%) on the induction of forward mutation at the thymidine-kinase locus in L5178Y mouse lymphoma cells. Used doses of 1,4-dimethylnaphthalene (purity 98.8%) were based on a range finding study with doses up to 1 mg/mL, which resulted in cytotoxicity at doses ≥ 100 µg/mL in the presence of S9 and doses ≥ 33 µg/mL in the absence of S9. The dose levels selected to measure mutation frequencies at the *tk*-locus were: 1, 5, 10, 20, 30, 35, 37.5 and 40 µg/mL exposure medium in the absence of S9 and 50, 75, 100, 150, 170, 200, 210 and 220 µg/mL exposure medium in the presence of S9. Positive controls were methylmethanesulfonate (MMS) without S9 and cyclophosphamide (CP) with S9.

In the presence of S9, dose-related increases in the mutant frequency were observed (at precipitating dose levels) both in small and large sized colonies. Increases were more than three-fold (3.7-fold for small colonies and 4.0-fold for large colonies) at a dose of 170 µg/mL (survival 38% in exp 1 and 33% in exp 2) and outside the historical control data range. At higher doses of 200-220 µg/ml increases were less than three-fold. At these doses the relative total growth was dose-dependently further reduced to 12% compared to the total growth of the solvent controls.
Based on the results of the study 1,4-dimethylnaphthalene was concluded to be mutagenic in mouse lymphoma L5178Y in the presence of metabolic activation, but not in the absence of metabolic activation. It is noted that the positive effect was observed at precipitating dose levels.

1,4-dimethylnaphthalene (batch no: H5510; purity: 96.4%) was tested in an *in vitro* assay for Unscheduled DNA Synthesis in rat liver primary cell cultures (IIA 5.4/04). Five cultures/treatment were included. Two were used for cytotoxicity measurements, the other 3 for analysis of nuclear labeling. Six treatments, from 0.250 to 10 µg/mL (108.9 to 58.2% survival) were selected for analysis of nuclear labeling. The positive control was 2-acetylaminofluorene. The study report used as evaluation criteria an increase in the mean net nuclear grain count to at least five grains nucleus above the concurrent solvent control (2.32) and/or an increase in the percent of nuclei having five or more grains such that the percentage of these nuclei in test cultures is at least 10% above the percentage observed in the solvent control cultures (12.67%). This differs from the criteria in OECD Guideline 482 (1987) which uses a significant dose-related increase in radiolabel incorporation or a reproducible and statistically significant positive response for at least one of the test points.

At a concentration of 10 µg/mL some toxicity was observed (58.2%). The high dose of 10.0 µg/ml resulted in a slight increase in mean nuclear grains (NNG) and in the percentage of cells with ≥5 mean NNG (see Table below). This was within the evaluation criteria used within the study but was slightly outside of historical control range (NNG -0.48 to -2.11, % cells with >5 mean NNG 0.67-9.00). Since no statistical analysis was carried out and since no repeat study was performed to

determine the reproducibility of the finding at 10 µg/ml the result of the study is considered equivocal.

Table 23: Results of the *in vitro* UDS

Concentration µg/ml	**Mean Net Nuclear Grains (NNG)[1]**	**% Cells w/≥ 5 mean NNG[1]**	**Mean Cytograins**	**% Survival at 20 hours**
0	-2.68	2.67	16.17	100
0.250	-1.65	6.00	13.97	103
0.500	-1.37	3.33	12.45	103.2
1.00	-1.18	8.67	10.82	106.8
2.50	-2.77	3.99	16.36	108.9
5.00	-1.38	7.97	14.06	95.8
10.0	0.01	10.00	9.75	58.2
Positive control	7.35	63.33	12.35	89.4

[1] Average values for triplicate coverslips

In vivo data:

In an *in vivo* micronucleus study (IIA 5.4/05 and IIA 5.4/06) male and female CD-1 (ICR) mice (5/sex/dose) received a single dose of 1,4-dimethylnaphthalene (batch no: H5510; purity: 96.4%) in corn oil, by gavage in doses of 225, 450 or 900 mg/kg bw. Bone marrow was harvested at 24, 48 and 72 hr after treatment and bone marrow slides were made and analysed. Appropriate controls were used (solvent control and cyclophosphamide as positive control). The study was performed in 2 parts. In the first part, reported in 1993, 1000 polychromatic erythrocytes were scored for the incidence of micronucleated polychromatic erythrocytes results of the study. In the second part, reported in 2007, 2000 polychromatic erythrocytes were scored for micronuclei.

Approximately 1 day after dosing, 1 high-dosed female appeared prostrate with dyspnoea. One male and 1 female (high-dose) appeared languid with dyspnoea. Approximately 2 days after dosing, 2 males and 3 females (high-dosed) were found dead. 1,4-dimethylnaphthalene caused decreases in the PCE:NCE ratios at 48 and 72h as compared to 24h (statistically significant in females only), although PCE/NCE ratios for the treated groups were within the historical control range. In view of the mortalities and the above mentioned clinical signs, and the toxicokinetic studies showing that closely related naphthalenes are well absorbed from the gut and rapidly occur in blood following oral dosing, it is assumed that 1,4-dimethylnaphthalene in this study will have reached the bone marrow of the mice.

In the first part of the study (1993), 1,4-dimethylnaphthalene induced a statistically significant increase in micronucleated polychromatic erythrocytes in females at the low dose in the 48-hour harvest group only. This was considered biologically irrelevant, since at higher doses as well as at later sampling points no increases in micronucleated polychromatic erythrocytes were observed. In addition, values were within the historical response range. In the second part of the study (2007) 1,4-dimethylnaphthalene induced statistically significant increases in micronucleated polychromatic erythrocytes in females at the mid-dose in the 24-hour harvest group. This was considered biologically irrelevant, since at higher doses as well as at later sampling points no increases in micronucleated polychromatic erythrocytes were observed and again the values were within historical control range.

1,4-dimethylnaphthalene was concluded to be negative in the mouse bone marrow micronucleus assay.

In an *in vivo* unscheduled DNA synthesis assay (IIA 5.4/07) male Sprague Dawley rats (n=4/group) received a single dose of 1,4-dimethylnaphthalene (batch no: 14D03M01-02 (range-finding) and 14D06B01-01 (main study); purity: 98.4-98.6%) in corn oil, by gavage in doses of 500 or 1000 mg/kg bw. Doses were based on a range finding study in male and female rats with doses of 1000, 1400 and 2000 mg/kg bw, in which toxicity was observed at doses ≥ 1400 mg/kg bw. No clinical signs of toxicity were observed in rats dosed with 500 or 1000 mg/kg bw. Positive controls were 75 mg/kg 2-acetamidofluorene and 10 mg/kg dimethylnitrosamine.

1,4-dimethylnaphthalene did not induce an increase net grain count. One of the positive controls failed the acceptance limits for a positive control response. Nevertheless, a marked increase in net nuclear grain (NNG) value was observed compared to the concurrent vehicle control (almost 4-fold increase) with a clear percentage of cells in repair, indicating that an increase in unscheduled DNA synthesis could be detected by the assay. It was concluded that 1,4-dimethylnaphthalene does not produce induction of unscheduled DNA synthesis in rat liver.

Overall, while some in vitro tests were positive for gene mutation the *in vivo* study were clearly negative and therefore 1,4-dimethylnaphthalene was concluded to be non-genotoxic.

10.8.2 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP), Table 3.5.2.2, classification in Category 2 mutagen is based on:
- Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:
- Somatic cell mutagenicity tests in vivo, in mammals; or
- Other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays

1,4-dimethylnaphthalene was tested negative for gene mutation in 2 bacterial gene mutation assay, but was tested positively in an *in vitro* mammalian gene mutation study. In addition, an *in vitro* UDS assay was concluded to be equivocal. In contrast, in the available *in vivo* micronucleus and UDS assay 1,4-dimethylnaphthalene was negative. It is therefore concluded that 1,4-dimethylnaphthalene does not fulfil the criteria for classification for mutagenicity.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

No classification is proposed.

10.9 Carcinogenicity

Table 24: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
OECD 453 Deviations:	1,4-dimethylnaphthalene (Batch no: F243A040/	NOAEL general toxicity: 150 ppm (equal to 10 mg/kg bw/day) based on minimal karyomegaly in kidneys in females. NOAEL carcinogenicity: 3750 ppm (equal to 208 mg/kg bw/day).	IIA 5.3/01 Doc ID 02-154

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
histopathology report did not differentiate between interim and terminal kill Rat, Sprague-Dawley CD IGS, Crl:CD(SD) Interim: 20/sex/dose Terminal: 65/sex/dose	14D06B01-01, Purity: 98.7%) Dose levels: 0, 150, 500 and 3750 ppm (equal to 0, 8, 27 and 208 mg/kg bw/day in males and 0, 10, 33 and 247 mg/kg bw/day in females) Interim: 52 week Terminal: 104 week	No increase in neoplastic findings.	

Table 25: Summary table of other studies relevant for carcinogenicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Public literature, non-GLP Klimisch Score 2	1-methylnaphthalene (purity >97%)	B6C3F1 mice (50/sex/dose) 0, 0.075, 0.15% 1-methylnaphthalene for 81 weeks (average intake 75.1 and 71.6 mg/kg bw/day in the low dose group, and 143.7 and 140.2 mg/kg bw/day in the high dose group for females and males)	Increased pulmonary alveolar proteinosis at both dose groups (46.0 and 34.7% of females and 46.0 and 38.0% of males, respectively). Increased bronchiolar alveolar adenomas in males (26% and 24%). No difference in bronchiolar/alveolar carcinomas.	IIA 5.5/04 Cited in ATSDR 2005 (IIA 5.7/02)
Public literature, non-GLP Klimisch Score 2	2-methylnaphthalene (purity >97%)	B6C3F1 mice (50/sex/dose) 0, 0.075, 0.15% 1-methylnaphthalene for 81 weeks (average intake 50.3 and 54.3 mg/kg bw/day in the low dose group, and 107.6 and 113.8 mg/kg bw/day in the high dose group for females and males)	Increased pulmonary alveolar proteinosis at both dose groups (55.1 and 45.8% in females and 42.9 and 46.9% in males, respectively). Increased bronchiolar/alveolar adenomas and carcinomas in males (20.4% and 12.2%).	IIA 5.5/05 Cited in ATSDR 2005 (IIA 5.7/02)

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

A combined chronic toxicity/carcinogenicity study (IIA 5.3/01) was carried out in accordance with OECD 453 (1981). 1,4-dimethylnaphthalene was applied by diet at dose levels of 0, 150, 500 and 3750 ppm. Relatively low survival was seen in control, low-dose and mid-dose females (28-35%) compared to high dose females (48%). The most common cause of death was pituitary adenomas; the incidence of pituitary adenomas was similar across groups (treated and control) for each sex. For high dose males the survival was acceptable (60%). For high dose females the survival was 48% however as the study started with 65 animals the reduction of the survival still results in a sufficient number of animals surviving at the end of the study. As the high dose groups showed a sufficient survival, the study was considered suitable for evaluation of the carcinogenic properties of 1,4-dimethylnaphthalene. Dietary intake of 1,4-dimethylnaphthalene resulted in actual doses of 8, 27 and 208 mg/kg bw/day in males and 10, 33 and 247 mg/kg bw/day in females.

No treatment-related clinical signs or mortality were observed in the study. At ophthalmic examinations, no eye abnormalities were observed. In high-dose males and females a significant decrease in food intake was observed. At termination of the study, body weight was significantly reduced in high-dose males (14%) and females (25%).

Platelet count was significantly decreased in high dosed males at 3 and 12 months and in high-dosed females at 3 and 6 months. In addition, high-dosed females showed significant decreases in MCV, haemoglobin and MCH at 6 months and significant decreases in MCV, MCH, MCHC, haemoglobin and white blood cell count at 12 months. High dosed males also had a significantly reduced white blood cell count at 12 months. No relevant effects were observed in the other groups. At study termination, high-dosed females showed significant decreases in MCV and MCH. No further toxicological relevant changes in haematology were seen at 18 months and at study termination.

Plasma cholesterol was increased in mid dose females (12 months only), high dose females (3, 6, 12 and 18 months, and in high dose males (18 months only).

Relative liver weight was statistically significantly increased (>10%) at the high dose in both sexes. At the terminal kill, high-dose females showed a statistically significant decrease in absolute kidney weight (17%). Histopathological changes were observed in the kidney. At 52 weeks these changes included an increased incidence in minimal to mild karyomegaly of the cortical tubules in mid and high-dosed females and high-dosed males, and an increased incidence of proteinosis in the tubules of the papilla and minimal papillary necrosis in high-dosed males. At the high dose the incidence of alveolar histiocytosis was increased in animals of both sexes. In males of the high dose group the incidences of lymphoid depletion and erythrocytic accumulation in the mesenteric lymph node were increased. At termination of the study at 104/100 weeks, histopathological changes in the kidneys included increased incidences of renal infarction, papillary mineralization, papillary necrosis, cysts in the cortex, proteinosis, dilatation of the papillary tubules and chronic progressive nephropathy in the high-dose males and/or females.

No increased incidences in neoplastic lesions were noted at study termination. The neoplasms observed in the study were typical of those frequently present in aged Sprague-Dawley rats, and no test material-related changes were noted for the incidence of neoplasms. Therefore, the administration of 1,4-dimethylnaphthalene to male and female Sprague-Dawley rats did not cause carcinogenicity.

Information on other naphthalene compounds from an Agency for Toxic Substances and Disease Registry (ATSDR) evaluation on the toxicological profile for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene showed that 1-methylnaphthalene and 2-methylnaphthalene induceed bronchiolar/alveolar adenomas in mice (IIA 5.5/04 and IIA 5.5/05). No significant difference was observed in the incidences of bronchiolar/alveolar carcinomas between 1-MN-treated and control mice. For 2-MN, the incidences of total lung tumours, including bronchiolar/alveolar adenomas and

carcinomas, were significantly increased only at the lowest dose males (control 4.1%, mid dose 20.4%, high dose 12.2%). It is noted that no dose-response was observed. There was no effect on adenocarcinoma in males and no effect on lung adenomas of adenocarcinoma is females.

Information from public literature indicate that mice are markedly more susceptible than rats to the pulmonary findings caused by naphthalene. Mice exposed by inhalation to 10 or 30 ppm naphthalene for 2 years showed lung inflammation, but rats exposed to concentrations up to 60 ppm showed no lung inflammation (Abdo et al. 2001 (IIA 5.5/11; NTP 1992 (IIA 5.5/12), NTP 2000 (IIA 5.5/13). The species difference in lung susceptibility to naphthalene has been correlated with higher rates of formation of a specific enantiomeric epoxide (1R,2S-naphthalene oxide) in lung microsomes and isolated dissected airways of mice compared with rats (Buckpitt et al. 1992, 1995 (IIA 5.5/09 and IIA 5.5/14). The highest rates of naphthalene metabolism were observed in mouse lung and liver microsomal incubations. Rat, hamster and monkey lung microsomal preparations metabolized naphthalene at 12, 37, and 1%, respectively, of the rate observed in mouse lung. Rat, hamster, and monkey lung microsomes preferentially formed the 1S,2R-naphthalene oxide enantiomer and showed lower rates of formation of epoxides than mouse lung microsomes with ratios of 0.48, 0.61 and 0.12 in rat, hamster and monkey lung microsomes, respectively compared to mice (Buckpitt et al. 1992 IIA 5.5/09). Microsomes from human lymphoblastoid cells expressing recombinant human CYP2F1 also showed preferential formation of the 1S,2R-naphthalene oxide enantiomer over the opposite enantiomeric 1R,2S-naphthalene oxide (Lanza et al. 1999 (IIA 5.5/15).

1,4-dimethylnaphthalene has a lower formation of highly reactive epoxide intermediates compared to 1-methylnaphthalene and 2-methylnaphthalene (see toxicokinetic information in section 9). The binding of epoxide intermediates to glutathione leading to thionaphthols results in the formation of 1,4-dimethyl-methylthionaphthalene. This thiomethyl derivate of 1,4-DMN was reported in the study IIA 5.1/01 in small amounts after i.p administration (1.39% of total identified compounds), but was not detected after oral administration in the ADME studies. It is therefore considered that systemic pulmonary alveolar proteinosis is unlikely for 1,4-dimethylnaphthalene.

10.9.2 Comparison with the CLP criteria

No information is available regarding carcinogenicity in humans. Therefore category 1A is not applicable.

Classification in category 1B requires "*a causal relationship between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites*".

Classification in category 2 requires "*the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs*".

In the carcinogenicity study in rat with 1,4-dimethylnaphthalene carried out in accordance with OECD Guideline 453 no increased incidence in neoplastic lesions were observed.

Information on other naphthalene compounds from public literature for 1-methylnaphthalene, and 2-methylnaphthalene showed that 1-methylnaphthalene and 2-methylnaphthalene induced bronchiolar/alveolar adenomas in mice. However, literature data indicate a clear species difference in susceptibility of this findings with naphthalene compounds due to higher rates of formation of a specific enantiomeric epoxide (1R,2S-naphthalene oxide) in lung microsomes and isolated dissected airways of mice compared with rats. Rat, hamster, and monkey lung microsomes preferentially formed the 1S,2R-naphthalene oxide enantiomer and showed lower rates of formation of epoxides than mouse lung microsomes with ratios of 0.48, 0.61 and 0.12 in rat, hamster and monkey lung microsomes, respectively compared to mice. Microsomes from human lymphoblastoid cells expressing recombinant human CYP2F1 also showed preferential formation of the 1S,2R-naphthalene oxide enantiomer over the opposite enantiomeric 1R,2S-naphthalene oxide. Humans are therefore expected to be less susceptible to this findings compared to mice. In addition, 1,4-dimethylnaphthalene has a lower formation of highly reactive epoxide intermediates compared to 1-methylnaphthalene and 2-methylnaphthalene. The binding of epoxide intermediates to glutathione leading to thionaphthols results in the formation of 1,4-dimethyl-methylthionaphthalene. This thiomethyl derivate of 1,4-DMN was reported in the study IIA 5.1/01 in small amounts after i.p administration (1.39% of total identified compounds), but was not detected after oral administration in the ADME studies. It is therefore considered that systemic pulmonary alveolar proteinosis is unlikely for 1,4-dimethylnaphthalene.

As there were no treatment related effects on tumor formation in the available experimental animal study with 1,4-demethylnaphthalene, classification for carcinogenicity is not warranted.

10.9.3 Conclusion on classification and labelling for carcinogenicity

No classification is proposed.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 26: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Extended 1-generation OECD 443 Rat, Sprague-Dawley	1,4-dimethylnaphthalene Batch no: F243A040/14D06B01-01, purity: 98.4% Doses: 0, 500, 2000, 7500 ppm (equivalent to 40, 160, 510 mg/kg	Parental: NOAEL parental: 40 mg/kg bw/day, based on reduced liver weight and increased cholesterol. Developmental NOAEL 160 mg/kg bw/day, based on delayed vaginal patency, preputial separation and reduced body weight Reproductive NOAEL: 510 mg/kg bw/day (highest dose tested)	IIA 5.6/07 (Doc ID 10-593)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
24/sex/dose	bw/day) 2-week premating through to lactation.		

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

In an extended one-generation study 1,4-dimethylnaphthalene (98.4%) was administered, as an admixture in the diet, at target concentrations of 0, 500, 2000 and 7500 mg/kg diet to 24 parental Sprague-Dawley rats/sex/group for 2 weeks prior to mating, during the 2-week mating period, for up to 10 weeks for the parental males and through gestation, lactation and until scheduled necropsy for the parental females. F1 pups were exposed to 1,4-DMN during the lactation phase of the study and selected F1 offspring were exposed to the same concentration of the diet admixtures as the parental dams from rearing until scheduled sacrifice. The F1 offspring were subdivided into two Cohorts; Cohort 1 was treated until 13 weeks of age and then subjected to a complete necropsy, while Cohort 2 was utilized for immunotoxicity assessment around 8 weeks of age (T-cell dependant antibody response). Thyroid hormones (thyroxine and thyroid stimulating hormone) were determined in P and F1 animals (PND 4 and 26). Food consumption, body weights, body weight gain, reproductive performance, organ weights, clinical pathology and histopathology were evaluated during the study, along with offspring body weights (growth), measurement of anogenital distance, survival and developmental landmarks (vaginal patency and preputial separation for the F1 generation).

No test substance related mortality was seen during the study period, and no treatment-related changes in clinical signs were observed. Food consumption was significantly reduced in the high-dose group in the first days of treatment (approximately 60%), and significantly reduced throughout the study period, although less severe than in the first week. Reduced food consumption was likely due to palatability. In the mid-dose group, food consumption was slightly reduced, when compared to controls. Body weight (approximately 10% in males and 15% in females) and body weight gain (around 30%) were significantly reduced in the high dose animals, and is considered to be due to the reduced food intake and the related reduced body weight gain in the first week of treatment for males, and the reduced body weight gain throughout the study period for females. Increased absolute and relative liver weights were observed in parental males and the mid and high dose groups (> 10% for both absolute and relative weights at the mid dose, and > 20% in the high dose). In parental males absolute spleen weights were decreased at the high dose (17%), and in parental high dose females absolute and relative spleen weights were decreased (22 and 12%, respectively). In high dose parental males testes relative weights were slightly increased (114%), and in parental females absolute and relative adrenal weights were decreased (25 and 16%, respectively, in mid dose parental females only absolute adrenal weight was decreased (15%).

Reproductive performance and litter viability were unaffected by treatment. No treatment related changes in sperm morphology and oestrus cycle were observed. The high dose group showed the lowest number of implantation sites (10 vs. 11.7) and a reduced incidence of live births (9.6 vs 11.2). These changes were not statistically significant, but may have been a secondary effect to the maternal toxicity observed in this group. No significant differences in the percent loss of fetuses between implantation and delivery were observed. A single high dose dam had a non-viable litter with 100% fetal loss prior to

delivery, but at this incidence rate (1/23) the observation was considered within normal biological variation and unrelated to treatment. No statistically significant difference in offspring survival was detected between the treated and control groups. Viability and lactation indices were unaffected by treatment. In addition, there were no changes in sex ratio, and the average number of surviving pups by sex was similar across groups.

Litter body weights were significantly reduced in the high dose group on the day of birth; this trend persisted throughout lactation, increasing in severity, and continued after weaning. From PDN 7 to 21, litter body weights were reduced > 40% in both males and females of the high dose. Litter body weights were also reduced at the mid dose for both males (10-14%) and females (15-16%), and for females only at the low dose (-8%) at the end of the lactation period. Anogenital distance as measured in PND 4 was not significantly different in the treated groups when compared to control. Preputial separation was delayed in the mid and high dose group and vaginal patency was delayed in the high dose group. The delayed preputial separation and vaginal patency appeared to be related to the reduced fetal body weight (see Table below). The applicant provided historical control data for preputial separation, generated by the laboratory in the period 2007-2008. Preputial separation has been observed in historical controls to occur on average around PND 44 (range PND 41-50); as such the delay noted in the 2000 mg/kg group was within normal biological variation. Moreover, the values in controls in the study (average PND 37, range PND 35-41) and low dose group (average PND 38, range PND 35-41) appear to be rather low, compared to the historical controls.

Food consumption, body weight and body weight gain of F1 pups selected for Cohort 1 and 2 were significantly reduced in all dose groups during the first three weeks of independent living. This was also considered to be due to palatability. Thyroxine (T4) and TSH were measured in both the parental and F1 generations as well as in PND26 weanlings, and no significant treatment-related changes were observed. In the immunotoxicity assessment in F1 animals, no treatment related changes were observed. At clinical biochemistry, increased in GGT and cholesterol levels were noted in both males and females of the high dose parental and F1 generation. In addition, increased cholesterol was also noted at the mid dose group. Triglycerides were increased in the high dose parental and F1 females, while triglycerides were reduced in high dose F1 males. Creatinin was reduced in mid and high dose parental and F1 females, and in mid dose parental males only. In F1 males absolute and relative liver weight were increased in mid dose (both 118%) and high dose (110 and 138%, respectively). In F1 females relative liver weight was increased in mid dose (113%) and high dose (152%). Several absolute organ weights were decreased in F1 high dose animals (i.e. adrenals, spleen, pituitary), however, these decreases were considered to be associated to the reduced body weight at the high dose. No treatment-related findings were seen at macroscopy.

Based on the minimal changes in liver weight and cholesterol at the mid dose groups, the NOAEL for parental toxicity is set at 500 mg/kg food (equivalent to 40 mg/kg bw/day). The NOAEL for developmental toxicity can be set at 2000 mg/kg food (equal to 160 mg/kg bw/day), based on delayed vaginal patency and preputial separation, and reduced body weight. As no fertility effects were observed, the NOAEL for reproductive toxicity is set at 7500 mg/kg food (equal to 510 mg/kg bw/day).

Table 27: Summary table of effects on delay preputial separation and vaginal patency

Endpoint	**Dose (mg/kg food)**							
	0		**500**		**2000**		**7500**	
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**
Preputial separation (days)	37		38		40*		46*	
Pup bw at preputial separation (g)	161		163		168		144*	
Vaginal patency (days)		34		36		35		43*
Pup bw at vaginal patency (g)		118		122		118		105*

*Statistically significant.

Historical control data

Sprague-Dawley Male rats	Age (days)	Body weight (g)
Mean	44.7	229.5
SD	2.5	2.3
Min	41.0	191.0
Max	50.0	273.0
N	46	46

No adverse effects on the reproductive organs in the available repeated dose toxicity studies was observed (studies summarized in section 10.12). An increase in relative testes weight (+31%) was observed in the 90-day study in rats (IIA 5.6/02) but this was considered to be possible related to the reduced body weight at this dose level and no histopathological findings were observed.

10.10.3 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP), Table 3.7.2.2, classification as for effects on fertility is based on:

Category 1A:
Known human reproductive toxicant
Category 1B:
Presumed human reproductive toxicant largely based on data from animal studies
— clear evidence of an adverse effect on sexual function and fertility in the absence of other toxic effects, or
— the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects
Category 2:
Suspected human reproductive toxicant
— some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility and
— where the evidence is not sufficiently convincing to place the substance in Category 1 (deficiencies in the study).
— the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects

According to the CLP criteria classification as Repr. 1A is based on human data. No human data are available for 1,4-dimethylnaphthalene and therefore, classification as Repr 1A is not justified.

Since no effect on fertility or sexual function was found in the experimental animal studies the criteria for classification for cat. 1B and cat 2 are not met.

10.10.4 Adverse effects on development

Table 28: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
OECD 414 Deviations: none New Zealand White rabbits 23 females/dose	1,4-dimethylnaphthalene (batch 14D06B01-01, purity 98.4%) GD6-28, gavage Dose levels: 0, 25, 80 and 250 mg/kg bw/day.	NOAEL maternal: 80 mg/kg bw/day based on the decreased body weight and reduced food consumption. NOAEL developmental: 250 mg/kg bw/day (highest dose tested)	IIA 5.6/08, Doc ID 10-601

Table 29: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Public literature, non-GLP Klimisch Score 1.	2,6-di-isopropylnaphthalene (purity not reported)	ICR-JCL mice (10/dose Gavage treatment GD6-12 Dose: 0, 19.2, 192 mg/kg bw/day	No treatment related effects on developing fetus	IIA 5.6/01
Public literature, non-GLP Klimisch Score 1 (although unclear if 1-methylnaphthalene or 2-methylnaphthalene was tested)	methylnaphthalene (purity not reported)	Wistar rats (22-24/dose) Gavage GD0-19 at 0, 16, 63 and 250 mg/kg bw/day	No treatment related effects on developing fetus	IIA 5.6/06
EPA evaluation (limited information available on the conduct and the results of the study)	2,6-diisopropylnaphthalene (purity unknown)	rat (strain unknown, groups size unknown) Dose: 0, 50, 150 and 150 mg/kg bw/day	Maternal NOAEL: 50 mg/kg bw/day based on decreased body weight and food consumption Developmental NOAEL: 150 mg/kg bw/day based on an	II 5.6/05

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			slightly increased incidence of skeletal alteration (fusion of cartilaginous bands in the cervical centra).	

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

In a developmental toxicity study female New Zealand White rabbits (23 per dose) were exposed to 0, 25, 80 and 250 mg/kg bw/day of 1,4-dimethylnaphthalane (batch 14D06B01-01, purity 98.4%) via gavage from gestation day 6 till 2 (IIA 5.6/08).

One rabbit in the high dose group was found dead on gestation day 21, likely related to the abortion that occurred one day earlier. Abortions occurred in all dose groups, without a dose-related response (incidence 2, 2, 1, 3). No treatment related changes in clinical signs, were observed in maternal animals. Food consumption (-45%) and body weight gain (-51% from GD6-9, -13% from GD9-12) were reduced in high dose maternal animals over gestation days 6-12. Absolute body weights were reduced when compared to controls in the high dose group on gestation days 9-18.

No treatment-related differences in litter viability were detected. A single statistically significant reduction in total implants was seen in the 80 mg/kg/day group. The number of total implants was also lower, but not significantly at 250 mg/kg/day group. The percent pre- and post-implantation loss was highest in the 80 and 250 mg/kg/day groups. Each of these groups had a single doe with a non-viable litter; exclusion of the non-viable litter showed that the post-implantation loss was similar across groups, while the pre-implantation loss remained higher in the 80 and 250 mg/kg/day groups even after exclusion of the non-viable litters. This change is considered toxicologically irrelevant as the exposure period is targeted to occur after implantation.

No treatment-related changes were noted in foetal weight and gross post mortem examination. External, visceral, cephalic and skeletal examinations revealed no treatment related variations or malformations.

The maternal NOAEL for 1,4-dimethylnaphthalene in rabbits was established to be 80 mg/kg bw/d based on decreased body weight gain and reduced food consumption. The NOAEL for developmental toxicity was 250 mg/kg bw/d.

Table 30: Summary table of pre- and postimplantation loss

Endpoint	Dose (mg/kg bw/day)			
	0	25	80	250
Non-viable litters	0	0	1	1
Pre-implantation loss (%)	2.6	3.4	8.3	10.1
Pre-implantation loss excluding single non-viable litter (%)	2.6	3.4	8.8	7.2
Post-implantation loss (%)	2.9	5.6	8.2*	8.8
Post-implantation loss excluding single non-viable litter (%)	2.9	5.6	3.4	2.3

* statistically significant

Some public literature information was available for other naphthalene compounds which are considered supplementary as a fully compliant guideline study is already available for 1,4-dimethylnaphthalene itself.

In a study from public literature (IIA, 5.6/01) pregnant ICR-JCL mice (four weeks, 18-20g) were treated by gavage from days 6-12 of gestation with 2,6-**di-isopropylnaphthalene** (purity not reported) at doses of 0, 19.2 and 192 mg/kg bw/day. Feed and water was supplied ad libitum. Each group within P_1 consisted of 20 dayms. Of these 10 were killed on day 18 of gestuation and organs were examined macroscopically. The number of implantation sites and absorbed dead embryos was examined. Body weights of the pups was measured. The pups were examined for the presence of absence of fetal abnormalities. Skeletal evaluation was carried out using Alizarin red S staining. The ten remaining dams were allowed to deliver and F1 offspring were obtained. The numbers of those alive and dead at birth, the sex, and external abnormalities were observed, and body weights measured. Live pups were kept with the dams during the laction period. Bodyweight of the pups was measured during this time On Day 21 after birth, touch (Pryer reaction), hearing (Haffner method), mobility (balance, gait), and other functions and senses were tested. Six weeks after weaning five males and five females were killed and major internal organs were observedmacroscopically, the masses of their internal organs measured, and histopathological investigationsconducted and on another five males and five females per group skeletal formation was examined using super soft X-ray photography. At ten weeks of age another 10 mice were mated and for the offspring the same examination was carried out as for the F1 offspring.

No significant effect on body weights occurred in dams. Through P1 and P2, no significant ($p>0.05$) differences were observed between the dosed groups and the respective control groups in the average numbers of implants per mouse, numbers of offspring per mouse, numbers of absorbed dead embryos per mouse, or average body weights of the fetuses per mouse, and in addition, no fetal external, intraoral or visceral abnormalities were seen within any group.

The EPA (2003, IIA 5.6/05) has reviewed a prenatal developmental toxicity study of 2,6-diisopropylnaphthalene in rats. The study was conducted at doses of 0, 50, 150, and 500 mg/kg bw/day. The NOAEL for maternal toxicity was considered to be 50 mg/kg bw/day based on decreased body weight and food consumption and the NOAEL for prenatal developmental toxicity was considered to be 150 mg/kg bw/day, based on decreased fetal body weight and a slightly increased incidence of a skeletal alteration (fusion of cartilaginous bands in the cervical centra).

In another study from public literature (Noda et al., 1982, IIA 5.6/06) pregnant Wistar rats (22-24/dose, 11 weeks at start of the study) were treated by gavage from gestation days 0-19 with **methylnaphthalene** (purity not reported, supplied by Tokyo Kasei Kogyo) at 0, 0.016, 0.063 or 0.25 ml/kg bw/day, equal to 0, 16, 63 and 250 mg/kg bw/day, assuming 100% purity and a specific gravity of 1. Olive oil was used oas solvent. Dosing was based on a preliminary study in 6 non-pregnant females. It is not clear whether 1-methylnaphthalene or 2-methylnaphthalene was used. Bodyweight and food and water intake was measured on each day and clinical signs were observed. On gestation day 20 the dams were killed and the effects of treatment with methylnaphthalene on the fetuses were investigated. The numbers of implantation scars, absorbed embryos, dead fetuses, and live fetuses were recorded. Various organs from the chest and stomach areas were dissected. The body weights of the live fetuses were measured, and they were examined for sex and external abnormalities. In addition, the numbers of corpora lutea in the dams' ovaries were examined. Approximately half of the live fetuses from each dam were fixed in 90% ethanol, and their skeletons stained with Alizarin red S. These were examined for degree of ossification and for the presence and absence of skelate abnormalities and variations. The remaining live fetuses were fixed in Bouin's solution, and were examined using the Wilson4) method for the presence or absence of visceral abnormalities.

No effect on bodyweight occurred. A slight reduction in food intake (<10%) was observed in the medium and high dose group dams, but from day 6 of gestation this recovered. Increased water intak was observed throughout gestation in the treatment groups. Since there were no changes in serum levels of urea nitrogen,
Na+, or K+, or in kidney weights, kidney failure was not considered, and the cause of these increases was not known.No treatment-related effects on the developing fetuses were reported.

The results of these studies do not impact the overall conclusion for 1,4-dimethylnaphthalene.

10.10.6 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP), Table 3.7.2.2, classification as for effects on development is based on:

Category 1A:

Known human reproductive toxicant

Category 1B:

Presumed human reproductive toxicant largely based on data from animal studies

— clear evidence of an adverse effect on development in the absence of other toxic effects, or

— the adverse effect on development is considered not to be a secondary non-specific consequence of other toxic effects

Category 2:

Suspected human reproductive toxicant

— some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on development and

— the evidence is not sufficiently convincing to place the substance in Category 1 (deficiencies in the study).

— the adverse effect on development is considered not to be a secondary non-specific consequence of the other toxic effects

According to the CLP criteria classification as Repr. 1A is based on human data. No human data are available for 1,4-dimethylnaphthalene and therefore, classification as Repr 1A is not justified.

In the developmental toxicity study in rabbits no relevant adverse effects on development were observed. In the 2-generation study (see 10.10.2) a delay in preputial separation in the mid and high dose males and vaginal opening in the high dose females was observed. The effects occurred in the presence of maternal toxicity in the form of reduced body weight (-15%), reduced body weight gain (-30%), reduced food consumption (-91%), increased cholesterol, gamma-GT and triglycerides, and increased liver, spleen and adrenal weight at the high dose group. In the mid dose maternal toxicity consisted of reduced food consumption (-11%), changes in liver weight and cholesterol. The delay in preputial separation and vaginal opening therefore appears to be secondary to maternal toxicity which is further supported by the fact that the finding seems to be related to a reduced body weight of the pups. The body weight at preputial separation and vaginal patency was the same or lower than in the control. In addition, there was no effect on anogental distance or other parameters which would be consistent with altered androgenicity or estrogenicity. It is therefore concluded that these findings are considered secondary to the maternal toxicity and do not warrant classification.

10.10.7 Adverse effects on or via lactation

No specific study carried out, see summary of the 2-generation study in section 10.10.2.

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

No specific study carried out, see summary of the 2-generation study in section 10.10.2.

10.10.9 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP), Table 3.7.2.2.2, classification for lactation effects is based on:

(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.

In the 2-generation study the severity of pup weight decreases increased throughout the lactation period. At birth pup weight was only 8% decreased in the high dose compared to control with no significant effect occurring in the mid dose. At PND 4 pup weight was already reduced by 21-22% in the high dose while at PND 14 pup body weight was reduced by 45-56% in the high dose and also in the mid dose by 14-16%. However, it is noted that this effect was observed in the presence of maternal toxicity (i.e. reduced food consumption, increased liver weight, increased cholesterol). Therefore, these effects on pup growth are considered secondary to the maternal toxicity and are not further taking into account for classification for adverse effects on or via lactation.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

No classification proposed.

10.11 Specific target organ toxicity-single exposure

Table 31: Summary table of animal studies on STOT SE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference

FIFRA 152-10 (in line with OECD 401) Deviations: none Rat, Sprague-Dawley (Crl:CD®BR) 5/sex/dose	1,4-dimethylnaphthalene (Batch H5510, purity 96.4%) Single oral gavage dose, Dose levels: Part 1: 750, 1000, 2500 mg/kg bw Part 2: 1300, 1700, 2100 mg/kg bw Part 3: 2000, 2300 and 2500 mg/kg bw	Mortality at 1700 mg/kg bw/day and higher. Clinical signs: hypoactivity, ataxia, coma, irritability, chromodacryorrhea, lacrimation, salivation, redness around the nose and/or eyes, wet/discoloured inguinal fur, coldness to the touch, hunched posture, diarrhoea, hair loss and discoloured paws (see Annex 1 for details).	IIA 5.2/01, Doc ID L08456, study 6,7,8
FIFRA 152-11 (in accordance with OECD 402) Deviations: none Rabbit, New Zealand/White 5/sex	1,4-dimethylnaphthalene (batch H5510, purity 96.4%) Single dermal dose (occluded)	No mortality No systemic signs of toxicity.	IIA 5.2/02, Doc ID L08456, study 4
FIFRA 152-12 (in line with OECD 403) Deviations: temperature outside of 22 ±2°C range (25-26°C) Rat, Sprague-Dawley (Crl:CD®BR) 5/sex	1,4-dimethylnaphthalene (batch H5510, purity 96.4%) Inhalation 4 h, whole-body Dose: 5 mg/L (achieved conc. 4.16 mg/L) MMAD: 2.82 µm	Mortality: 1 out of 5 animals at 4.16 mg/L Clinical signs: dyspnea, prostration, ptosis, hypoactivity, discolouration around the mouth and/or nose and wet inguinal fur, tremors, red nasal and ocular discharge.	IIA 5.2/03, DocID L08456L001

10.11.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

See section 10.1 to 10.3 for summaries on the acute studies.

10.11.2 Comparison with the CLP criteria

Comparison with Category 1 and 2:
According to Regulation EC No 1272/2008 (CLP) the following criteria apply for STOT SE Cat 1 and 2:

Category 1:
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.

Category 2:
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

Table 3.8.2 of the CLP Guidance indicates that the limits for category 1 from the animal studies are 300 mg/kg bodyweight for oral exposure, 1000 mg/kg bodyweight for dermal exposure and 1.0 mg/L/4h for inhalation exposure. For category 2 the limits are 2000 mg/kg bodyweight for oral and dermal exposure and 5.0 mg/L/4h for inhalation exposure. While clinical signs such as hypoactivity and salivation were observed in the acute oral toxicity at dose levels <2000 mg/kg bw/day there were no signs of specific target toxicity. Therefore, classification with Category 1 or 2 is not required.

Comparison with Category 3:
According to Regulation EC No 1272/2008 (CLP) the following criteria apply for STOT SE Cat 3:

Transient target organ effects
This category only includes narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above.

In the acute inhalation study dyspnoea was observed on day 0 only and nasal discharge was observed during 1-2 after treatment. The effects were not considered severe enough to warrant classification with STOT SE 3. In the acute oral toxicity study ataxia was observed at a high dose level of 2500 mg/kg bw/day. Since there were no other sign of narcotic effects classification with STOT SE 3 is not warranted.

10.11.3 Conclusion on classification and labelling for STOT SE

No classification proposed.

10.12 Specific target organ toxicity-repeated exposure

Table 32: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
90-day study OECD408 Deviations: water consumption not measured, blood clotting potential not analysed Rat, Sprague-Dawley (CRL:CD(SD)IGSBR) 10/sex/dose	1,4-dimethylnaphthalene, batch 01C-01, purity 98.8% Doses: 0, 500, 2500, 10000 ppm (equal to 0, 32, 161 and 677 mg/kg bw/d in males and 0, 38, 186 and 747 mg/kg bw/d in females) 13-week exposure by diet	<u>10,000 ppm (677 mg/kg bw/day for males, 747 mg/kg bw/day for females):</u> • Clinical signs (alopecia, rough fur, discoloured fur, vaginal discharge) • Reduced body weight gain (-32-34%) • Reduced food consumption (-10-20%) • Reduced grip strength forelimb • Reduced Hb in females (-4%), MCH (-4%) and reduced MCHC in females (-3%) • Increased cholesterol (+37-97%), decreased triglycerides in males (-49%) • Increased relative liver weight in males and females (+26-62%) and absolute liver weight in females (+41%). Increased relative kidney (+18%). Increased relative testes weight (+31%) possible due to reduced body weight. • chronic progressive nephropathy (CPN) in kidneys <u>5000 ppm (161 mg/kg bw/day for males, 186 mg/kg bw/day for females)</u> • Clinical signs (discoloured fur) • Reduced body weight gain in males (-11%) • Reduced food consumption in males (-10%) • Increased cholesterol (+27-31%), decreased triglycerides in males (-29%) • Increased relative liver weight (+20%) <u>500 ppm (32 mg/kg bw/day for males, 38 mg/kg bw/day for females)</u> No adverse effects.	IIA 5.6/02, Doc ID 02-154

Chronic toxicity/carcinogenicity OECD 453 Deviations: histopathology report did not differentiate between interim and terminal kill Rat, Sprague-Dawley CD IGS, Crl:CD(SD) Interim: 20/sex/dose Terminal: 65/sex/dose	1,4-dimethylnaphthalene (Batch no: F243A040/ 14D06B01-01, Purity: 98.7%) Dose levels: 0, 150, 500 and 3750 ppm (equal to 0, 8, 27 and 208 mg/kg bw/day in males and 0, 10, 33 and 247 mg/kg bw/day in females) Administration via diet Interim: 52 week Terminal: 104 week	<u>3750 ppm (208 mg/kg bw/day for males, 247 mg/kg bw/day for females)</u> • Reduced body weight (-14 to 25%) • Reduced food consumption • Haematological findings (reduced Hb (-5%), reduced MCV (-9%), reduced MCH (-9%), reduced MCHC, decreased platelet count (-21%) • Increased cholesterol (+71%) • Increased relative liver weight (+42%), increased relative kidney weight (+15%) • Kidney nephropathy, papillary necrosis, karyomegaly tubuli, microabces, proteinosis, mineralization. Liver cysts, mesenteric lymph node depletion <u>500 ppm (27 mg/kg bw/day for males and 33 mg/kg bw/day for females):</u> • Increased cholesterol (+30%) • Kidney, karyomegaly tubuli <u>150 ppm (8 mg/kg bw/day for males and 10 mg/kg bw/day for females):</u> No adverse findings	IIA 5.3/01 Doc ID 02-154
Extended 1-generation OECD 443 Rat, Sprague-Dawley 24/sex/dose	1,4-dimethylnaphthalene Batch no: F243A040/14D06B01-01, purity: 98.4% Doses: 0, 500, 2000, 7500 ppm (equivalent to 40, 160, 510 mg/kg bw/day) 2-week premating through to lactation.	<u>7500 ppm (510 mg/kg bw/day)</u> • Reduced body weight (-15%) and body weight gain (-30%) • Reduced food consumption (-61%) • Increased cholesterol (+123%), gamma-GT and triglycerides (+41%) • Increased liver weight (+52%), decreased absolute spleen weight (-22%, P-generation only) increased absolute testes weight (+14%, P-generation only), decreased absolute and relative adrenal weight (-25%, P-generation only) • Moderate kidney karyomegaly in 1 adult male <u>2000 ppm (160 mg/kg bw/day)</u> • Reduced food consumption (-11%) • Increased cholesterol (+45%) • Increased liver weight (>10%) <u>500 ppm (40 mg/kg bw/day)</u> No treatment related adverse findings.	IIA 5.6/07 (Doc ID 10-593)

10.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

Table 33: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days

Study reference	Effective dose (mg/kg/d)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
IIA 5.3/01 Doc ID 02-154	208 mg/kg bw/day	52 weeks (effects on the kidney already occurred in interim sacrifice)	843.6 mg/kg bw/day	No

Rats (10/sex/dose) were given 0, 500, 2500 or 10.000 ppm 1,4-dimethylnaphthalene for 13 weeks in their diet. Two additional groups (control and high dose group, 10/sex) were held for an additional 28 days to evaluate the recovery potential from 1,4-dimethylnaphthalene-induced effects (0 and 10.000 ppm). Full histopathology (including reproductive organs) was confined to controls and high dose animals, except for kidneys which were histopathologically examined in all dose groups.

No treatment-related deaths were observed during the study. No treatment-related clinical signs were observed, except for discoloured inguinal fur. Body weight gain was statistically significantly reduced by 32-34% in both sexes at the high dose. A statistically non significant decrease in body weight gain of 11% was observed in males of the mid-dose group. A dose-related decrease in food intake was observed: high-dosed rats (both sexes) consumed significantly less food throughout the study (10-20% decrease); mid-dosed male rats ate significantly less in the first 10 weeks (10% decrease). Effects on haematological and clinical chemistry parameters were mainly observed in the highest dose group and consisted of changes in haemoglobin, MCH, MCHC, A/G ratio, globulin, BUN, glucose, cholesterol and triglyceride levels. Cholesterol was increased in high-dosed females and in mid- and high-dosed males. The reduction in triglyceride levels in males may be related to the poor nutritional state. Increased relative organ weights (111-163% compared to controls) were observed in both males and females of the highest dose group and in males of the mid-dose group for a number of organs (including testes), which may be, at least partly, related to the observed decreased body weight gain in the highest dose group. No gross pathological findings were observed. Microscopically, changes were observed in the kidneys and included an increased incidence and severity of chronic progressive nephropathy (CPN) in the high-dose group. The effects were more pronounced in males than in females.

For the summaries of the chronic toxicity study and 2-generation study it is referred to section 10.9.1 and 10.10.2. In the chronic toxicity study effects on the kidney, including nephropathy, papillary necrosis, were observed at high dose levels of 208 mg/kg bw/day in males and 247 mg/kg bw/day in females. These effects were already observed in the interim sacrifice. However, they occurred at dose levels not relevant for classification with STOT-RE. In the 2-generation study no effects occurred that are relevant for STOT-RE.

10.12.2 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP) the following criteria apply for STOT RE:

Category 1 (H372):
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 repeated exposure.
Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of:
reliable and good quality evidence from human cases or epidemiological studies; or observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations.
Equivalent guidance values for different study durations (oral only, since dermal and inhalative studies not relevant in this case):
Rat:
28-day: ≤ 30 mg/kg bw/d
90-day: ≤ 10 mg/kg bw/d

Category 2 (H373)
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 repeated exposure.
Substances are classified in Category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations.
Equivalent guidance values for different study durations (oral only, since dermal and inhalative studies not relevant in this case):
Rat:
28-day: ≤ 300 mg/kg bw/d
90-day: ≤ 100 mg/kg bw/d

No adverse findings were observed in the repeated dose studies that would trigger classification with STOT-RE. In the 90-day study the LOAEL was 161 mg/kg bw/day for males and 186 mg/kg bw/day and the effects observed at this dose level were not severe. In the chronic toxicity study effects on the kidney were observed, including papillary necrosis, but only at a high dose level of 208 mg/kg bw/day for males and 247 mg/kg bw/day for females which would therefore not trigger classification. In the extended one-generation study no effect was observed that would trigger STOT-RE classification. Similarly in the developmental toxicity study in rabbits only effects on decreased body weight and reduced food consumption was observed. Therefore, it is concluded based on the results of the studies classification with STOT-RE is not warranted for 1,4-dimethylnaphthalene.

10.12.3 Conclusion on classification and labelling for STOT RE

No classification proposed.

10.13 Aspiration hazard

Table 34: Summary table of evidence for aspiration hazard

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
FIFRA § 63-18 Viscosity	1,4-dimethylnaphthalene	Measured.	Mean viscosity was 6 mPa s at 12 rounds per minute and 6 mPa s at 30 rounds per minute at 25 °C. The kinematic	IIA 2.1/02 Doc ID 4373-93-0226-AS

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			viscosity is 6 mPa.s / 1.014 = 5.9 mm^2/s.	

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

The viscosity of 1,4-dimethylnaphthalene was measured at 25°C using a Brookfield viscometer (IIA 2.1/02). No justification was provided on why the study was conducted at 25ºC The analysis was repeated with the same sample aliquot. A viscosity standard was also analysed in replicate. Mean viscosity was 6 mPa s at 12 rounds per minute and 6 mPa s at 30 rounds per minute at 25 °C. The kinematic viscosity is 6 mPa.s / 1.014 = 5.9 mm^2/s.

10.13.2 Comparison with the CLP criteria

According to Regulation 1272/2008 a substance should be classified for aspiration toxicity when:

Substances known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard

A substance is classified in Category 1:

(a) based on reliable and good quality human evidence or

(b) if it is a hydrocarbon and has a kinematic viscosity of 20.5 mm^2/s or less, measured at 40 ºC.

The kinematic viscosity of 1,4-dimethylnaphthalene was found to be 5.9 mm^2/s. As this is below 20.5 mm^2/s classification for aspiration toxicity is required.

10.13.3 Conclusion on classification and labelling for aspiration hazard

Harmonised classification proposed (Asp. Tox 1, H304)

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

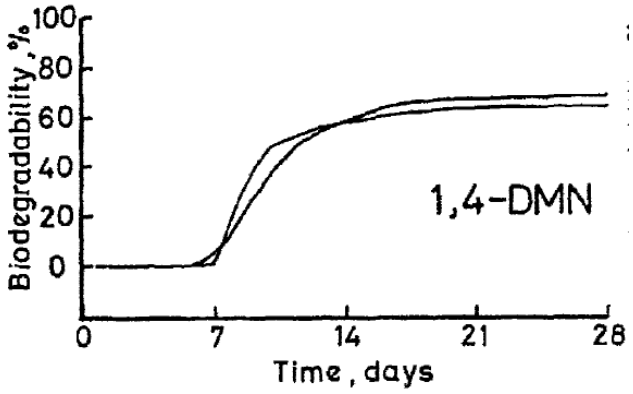
Table 35: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Ready biodegradability OECD301C (EEC C.4-F) 1,4-dimethylnaphthalene (purity not reported)	Degradation: >60% within 28 days). Readily biodegradable	Non-GLP, public literature study MITI (I) test Ri = 2	Study IIA 7.7/01
Water-sediment degradation	-	Study not acceptable	Study IIA 7.8/01 Doc ID 535E-102

Method	Results	Remarks	Reference
OECD 308 1,4-dimethylnaphthalene (batch 3501-032, purity 97.1%)		Rapid disappearance from water-sediment due to volatility of 1,4-dimethylnaphthalene Ri = 3	
Photchemical degradation (QSPR model) Non-guideline	Photolytic half-life 3.2-12.8 h	Non-GLP, public literature study QSAR generated endpoint	Study IIA 7.6/01

11.1.1 Ready biodegradability

In a public literature study the biodegradability of 1,4-dimethylnaphthalene was evaluated using the MITI (I) test method (IIA 7.7/01). Inoculated test medium is dosed with 100 mg/kg of 1,4-DMN as the nominal sole source of organic carbon. Degradation was followed by analysing dissolved oxygen over a 28-day test period at 25°C. Measurements of dissolved oxygen were performed on two test chambers from the control, reference (aniline), and treatment groups on days 7, 14, 21 and 28.
The system used in the MITI test is a closed system under pressure which should prevent volatilisation from the system. The shape of the degradation curve indicates a proper biological degradation.
The results indicate that the inoculum was active by degrading the reference substance within the acceptable range (at least 40% after 7 days and 65% after 14 days). In this study, more than 60% degradation of 1,4-dimethylnaphtalene (60% of theoretical maximum) is achieved. 1,4-dimethylnaphtalene was concluded to be readily biodegradable (please note that the 10-d window does not apply for the OECD 301C test). Although an abiotic control –as laid down in OECD 301 C- is not included. The shape of one of the degradation curves indicates a proper biological degradation (see below). The other curve, where loss due to biodegradation increases steeply after 7 days, may indicate (some) effect of volatilization in the first few days. However, a full biphasic pattern, which would be expected in case volatialization was a major process is not observed. Overall, the study is conducted well and the results can be considered reliable; Klimisch score = 2 (public literature).



11.1.2 BOD_5/COD

No data available.

11.1.3 Hydrolysis

No experimental data are available. The solubility of 1,4-DMN in water is very low (5.1 mg/L at 25°C). Based on the molecular structure, hydrolytic degradation of 1,4-DMN is expected to be very low in

aquatic systems. Estimation of a DT50 for hydrolysis is not possible with EPIWeb 4.0 (HydroWin). EUSES 2.1 estimation of DT50 = 5.27 x 10^5 day (20°C).

This estimation is made based on a model used for other purposes, using QSAR estimates and assumptions and is therefore considered not reliable. Klimisch score = 3.

11.1.4 Other convincing scientific evidence

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

No further data needed.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No data available.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

Water-Sediment

A water-sediment degradation study was submitted (Study IIA 7.8/01). The study showed poor recoveries and in additional aerobe mineralisation/volatilisation tests it was shown that 1,4-DMN was being lost, potentially to the rubber stopper assemblies used to affix the test chambers to the mineralisation apparatus. In the third additional experiment to the water-sediment study, it was demonstrated that 46% of the radioactivity had escaped to the gaseous phase after 2 days (75% after 23 days). Although the composition of the medium in this additional experiment was not the same as in the main study, rubber stoppering was not used to minimize losses. Therefore, the additional experiments demonstrate that the high loss of radioactivity from the water-sediment phase in the main test was largely due to volatilisation, instead of to adsorption to the rubber stoppers. Therefore, there would be minimal opportunity for retention by sediment followed by metabolite formation, as the extensive volatility would preclude such from happening. The study is considered unreliable for classification purposes (Ri = 3)

Soil

No fully adequate experimental data are available on biodegradation of 1,4-DMN in soil. Some indications based on literature references were submitted (see Annex 1 for details). No reliable DT50 value for 1,4-DMN can be derived from the submitted data.

Some indications based on literature studies were submitted (IIA 7.1/01, IIA 7.1/02 IIA 7.1/03, IIA 7.1/04 and IIA 7.1/05).

In the first study (IIA 7.1/01) the microbial oxidation of 1,4-DMN by isolated bacteria (*Alcaligenes* sp. strain D-59 and *Pseudomonas* sp. strains D-87 and D-186) was investigated. Strain D-87 grew well on (amongst others) 1,4-DMN as the sole source of carbon and energy and accumulated 4-methylnaphthalene-1-carboxylic acid from 1,4-DMN. The information points at the possibility of metabolisation of 1,4-DMN by soil micro-organisms.

In the second study (IIA 7.1/02) evaluated the metabolism of 2,6-DMN by flavobacteria. Flavobacteria that were able to grow on 2,6-dimethylnaphthalene (2,6-DMN) were isolated from soil. Most were able to oxidize a broad range of aromatic hydrocarbons after growth on 2,6-DMN at rates comparable to that of the oxidation of 2,6-DMN itself. One small group was neither able to grow on naphthalene nor able to oxidize this compound after growth on 2,6-DMN, but metabolised 2,6-DMN by a pathway which converged with that previously described for naphthalene metabolism in *Pseudomonas*. No information on 1,4-DMN was reported in this study.

The third study (IIA 7.1/03) concerned the composting of hazardous waste and hazardous substances.The results demonstrate that composting can be used to decrease the concentration of hazardous organic substances, but that the more volatile constituents may vaporize, rather than degrade. When the effects of volatilization were removed, the half life based solely on biodegradation ranged from 7.0 - 11.6 days for DMN. It was not reported which congener it was. Therefore the results can only be used as indicative values.

A fourth study (IIA 7.1/04) was submitted concerning the laboratory scale in-vessel composter designed for volatile emissions analysis. Volatilisation of DMN is mentioned sideways in this study. The information presented is not considered relevant.

In the fifth study (IIA 7.1/05) pathways of aerobic bacterial degradation of methylated naphthalenes in soil were studied. It was reported that *Paucimobilis* 2322 formed 3,6-dimethylsalicylic methyl ester and 4-methyl-1-naphtoic acid methyl ester from 1,4-DMN. The information points at the possibility of metabolisation of 1,4-DMN by soil micro-organisms, but cannot be used to quantify biodegradation in soil.

From the various references, if taken together, it is evident that 1,4-dimethylnaphthalene will be degraded by soil micro-organisms, that 4-methylnaphthalene-1-carboxylic acid is the most important degradation product in soil, and that volatility is a major route of disappearance from soil.

11.1.4.4 Photochemical degradation

Photolysis in water

In a public literature study Weterings (2004, IIA 7.6/01) used a QSPR model to predict the photolytic half-live of 1,4-DMN, based on quantum chemical descriptors. The developer of the model (Chen et al., 2000, 2001) developed the model based on 13 closely related polyhydrocarbons. Inclusion of 1,4 DMN in the model resulted in a photolytic half-live of 6.4 hours.
In addition, a literature study that aimed to describe the development of the QSPR model used in the Weterings study was submitted. This study was based on the observed and predicted photolytic half-lives for 1-methylnaphtalene and 2-methylnaphtalene. The study shows that the model predicts the photolytic half-live to structural analogies of 1,4-DMN with a uncertainty factor of 2. In addition, a study by Fukada *et al.* (*1988*) showed that the degradation rates of of alkylnaphthalenes from monomethylnaphthalene to diisopropylnaphthalene are actually very similar. Based on this, the RMS concludes that the photolytic half-life of 1,4-DMN in water ranges from 3.2 – 12.8 hours. Photolysis studies may be used to evaluate whether under field conditions metabolites may be formed that are not detected in water/sediment studies, which are performed in the dark.

Based on the above and considering the Guidance given in QSAR methods for degradability is presented in IR&CSA, Chapter R.7.9.3.1. and the document 'Practical report – How to use and report (Q)SARa 3.1 (July, 2016), the evaluator notes that the available information is not sufficient to judge the algorithm nor the statistics of this QSAR. Taking this, and the Guidance in consideration the above QSAR may be useful as supplementary data but **cannot be the key endpoint for classification.**

11.2 Environmental transformation of metals or inorganic metals compounds

11.2.1 Summary of data/information on environmental transformation

Not relevant for this dossier.

11.3 Environmental fate and other relevant information

Vapor pressure:
1,4-dimethylnaphthalene has a high vapour pressure of 2.50 Pa at 25°C (see Table 7) and therefore concluded to be volatile.

Adsorption/desorption from soil:
In a public literature study (Klimisch score = 2) the soil sorption coefficient for 336 hydrocarbon and organic chemicals in water were reported (IIA 7.4/01). The non-linear group contribution method was used to estimate the soil sorption coefficient when experimental Koc values were not available. A comparison of calculated and experimental values for the soil sorption coefficient shows general agreement of calculated and experimental values for different organic chemicals. The Koc value for 1,4-DMN was estimated to be 4230 L/kg.

In addition the Koc was estimated to be 4139 L/kg using EPIWIN (EPIWeb 4.0), using Molecular Connectivity Indices Method. The Koc using the experimental log Kow of 4.37 is 6199 L/kg. Based on this information the results from the study are in line with the calculated values and the Koc of 4230 L/kg.

11.4 Bioaccumulation

Table 36: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
No guideline reported. *Cyprinodon variegatus* (sheepshead minnows) 36-day continuous flow 1,3-dimethylnaphthalne (purity not reported)	BCF: 5751 L/kg	non-GLP, public literature study Study carried out with 1,3-dimethylnaphthalene which was considered comparable to 1,4 DMN. Ri = 2	IIA 8.2/07

11.4.1 Estimated bioaccumulation

No data.

11.4.2 Measured partition coefficient and bioaccumulation test data

Adult sheep head minnows (*Cyprinodon variegatus*; 158 females and 129 males, mean weight 2.47 ± 1.23 g and mean length 4.7 ± 0.8 cm at sampling times) were exposed to two concentrations of PAH mixtures in seawater (a stock solution was prepared in acetone) in a continuous-flow system (IIA 8.2/07). The fish were exposed for a period of 36 days, followed by 8 days of depuration. The PAHs studied were pure naphthalene, 2-methylnaphthalene, 1,3-dimethylnaphthalene, 2-isopropylnaphthalene, phenanthrene, pyrene, 9-methylphenanthrene, and 9-ethylphenanthrene. The 1,3-dimethylnaphthalene concentrations were 2.74 ± 0.73 µg/L and 26.67 ± 9.19 µg/L. Bioconcentration factors (BCFs) for individual PAHs were estimated from the ratio of k_1 to k_2 by use of a first-order, one-compartment kinetics model and also directly from PAH concentrations in fish tissue and water samples (from sampling days 4, 7 and 36).

Naphthalene and its three alkylated isomers revealed peak levels within 4 d in both treatments except for the low-exposure concentration of C2 - and C3 -alkylated naphthalene, which reached maximum at day 7. Uptake rate constants (k_1) for the naphthalenes increased with increasing degree of alkylation and log value of the octanol/ water partition coefficient (Kow), whereas k_1 values for three- and four-ring PAHs were lower despite their high log Kow values. Elimination rate constants (k_2) for the homologue series of naphthalenes and phenanthrenes generally increased with decreasing degree of alkylation and log Kow values. However, the depuration time did not directly correlate with the molecular size for nonalkylated PAHs.

A significant positive correlation was determined between log BCFs and log Kow values for the series of C0- through C3-naphthalenes at both low (r^2 = 0.985, p = 0.0077) and high (r^2 = 0.956, p = 0.022) exposures. The two exposure levels revealed minor variations in k_1 and k_2 values for parent PAHs and in the temporal pattern of PAH metabolite concentrations in bile. The present results indicate that the presence and nature of alkyl groups have a significant influence on the kinetics and metabolism of PAHs in fish.

For 1,3-dimethylnaphthalene, a wet weight-based bioconcentration factor of 4000 L/kg was determined at a concentration of 2.74 µg/L and 8000 L/kg at 26.7 µg/L. The geometric mean of the BCF values for both concentrations results in an overall BCF value for 1,3-dimethylnaphthalene of 5751 L/kg. Normalized BCF values were not reported.

The study is conducted well and the results can be considered reliable; Klimisch score = 2 (public literature).

No specific study was carried with 1,4-dimethylnaphthalene. However, study IIA 8.2/07 showed that there is a correlation between the log Kow and BCF value. The log Kow values of 1,3-dimethylnaphthalene and 1,4-dimethylnaphthalene are very similar. A published literature study (Dimitrou-Christides, 2003) which on the basis of an accepted methodology (GC and HPLC retention time comparison for estimating several physical-chemical characteristics) established several partition coefficients for a number of methylated naphthalenes, including 1,3-DMN and 1,4-DMN. The estimated logKow values for 1,3-DMN and 1,4-DMN were 4.27 and 4.22 resp. The article also stated that LogKow increases with the number of methyl groups (1,3-DMN and 1,4-DMN have an equal number of methyl-groups). Since the LogKow is a driving potential for the BCF value it is concluded that the BCF value of 5751 can be extrapolated to 1,4-dimethylnaphthalene.

11.5 Acute aquatic hazard

The acute aquatic toxicity studies of 1,-4-dimethylnaphthalene were assessed in the Draft Assessment Report (October 2012) prepared in the context of the approval, under Reg. (EC) 1107/2009. Studies considered valid in the and DAR (reliability score of 1 or 2) have been included in this report. All studies were carried out under GLP unless indicated otherwise and in accordance with OECD guidelines. Minor deviations were noted in one study but these did not affect the overall reliability of the studies. The deviations are included in the summaries were relevant.

Table 37: Summary of relevant information on acute aquatic toxicity

Method	Species	Test duration	Test material	Results[1]	Remarks	Reference
FIFRA 72-1, OECD 203, EEC C.1	Rainbow trout (*Oncorhynchus mykiss*)	96 h	1,4-dimethylnaphthalene, batch H5510, purity 96.4% Dose levels: 0, 0.32,	LC_{50} = 0.67 mg/L Mean measured	-	IIA 8.2/01, DocID 93-10-4955

			0.54, 0.90. 1.5 and 2.5 mg a.s./L			
OPPTS 850.1075 (= OECD 203, EEC C.1) Deviations: concentrations of the solvent are not reported.	Fathead minnow (*Pimephales promelas*)	96 h	1,4-dimethylnaphthalene, batch 01C-01, purity 98.8% Dose levels: 0, 0.25, 0.50, 1.0, 2.0, 4.0 and 8.0 mg a.s./L	LC_{50} = 1.4 mg a.s./L Mean measured.	-	IIA 8.2/02 DocID 535A-101A
FIFRA 154-9, OECD 202, EEC C.2	*Daphnia magna*	48 h	1,4-dimethylnaphthalene, batch H5510, purity 96.4% Dose levels: First test: 0.16, 0.26, 0.43, 0.72, and 1.2 mg as/L Second test: 0.65, 1.1, 1.8, 3.0, and 5.0 mg as/L	EC_{50} = 0.54 mg a.s./L Mean measured	-	IIA 8.3.1/01 DocID 93-104951
OECD 221	*Lemna gibba*	7 d	1,4-dimethylnaphthalene, batch 01C-01, purity 98.8% Concentration: 0.16, 0.31, 0.63, 1.3, 2.5 and 5.0 mg/L	I_rC_{50} 1.1 mg/L Mean measured. Mean measured.	-	IIA 8.6/01 DocID 535A-103
OPPTS 850.5400, OECD 201, EEC C.3	*Pseudokirchneriella subcapitata*	96 h	1,4-dimethylnaphthalene, batch 01C-01, purity 98.8% Concentration: 0.028, 0.056, 0.11, 0.23, 0.45 and 0.90 mg a.s./L	72-h E_bC_{50}: 0.32 mg a.s./L 72-h E_rC_{50}: 0.62 mg a.s./L Mean measured.	The validity criteria of OECD 201 were not met with respect to control growth.	IIA 8.4/01 DocID 535A-102

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

11.5.1 Acute (short-term) toxicity to fish

Rainbow trout (*Oncorhynchus mykiss*), mean wet weight 1.5 g (range 0.80 to 2.84 g); mean total length 50 mm (range 42 to 63 mm), were exposed to a concentration range of 1,4-dimethylnaphthalene, batch H5510, purity 96.4%, in a flow-through test (6.6 volume replacements/aquarium every 24 h) (IIA 8.2/01). The study was carried out in accordance with OECD 203. A stock solution of the test substance was prepared in acetone. Nominal test concentrations 0.32, 0.54, 0.90, 1.5, and 2.5 mg as/L a control and a solvent control (0.5 mL/L acetone) Test concentrations were based on the results of a range-finding test. Two replicates with ten fish each, 15 L water per test aquarium.

Mean measured concentrations were 0.19, 0.22, 0.41, 0.75 and 1.2 mg/L. Measured test concentrations ranged from 40% to 58% of nominal test concentrations, but were constant during the test. At test

termination (96 hours), mortality of 100% was observed among rainbow trout exposed to the highest mean measured concentration (1.2 mg/L). Mortality of 5%, 5% and 45% was observed among organisms exposed to the 0.22, 0.41 and 0.75 mg/L test concentrations, respectively. In addition, sublethal effects (e.g., loss of equilibrium) were observed among all of the surviving fish exposed to these test concentrations.

The 96-hour LC_{50} was calculated to be 0.67 mg/L with a 95% confidence interval of 0.57 to 0.80 mg/L using the moving average angle method. The 48-h LC_{50} was 1.0 mg as/L, the 72-h LC_{50} was 0.89 mg as/L. The LC_{50} for 48 and 72 hours of exposure was based on probit analysis and nonlinear interpolation, respectively. The No-Observed-Effect Concentration (NOEC) was determined to be 0.19 mg/L. LC_{50} and NOEC values are based on mean measured test concentrations. Study is considered reliable and the endpoint is acceptable for classification.

Fathead minnow (*Pimephales promelas*), mean wet weight 0.062 g (range 0.035 to 0.12 g); mean total length 2.0 cm (range 1.7 to 2.5 cm), were exposed to a concentration range of 1,4-dimethylnaphthalene, batch 01C-01, purity 98.8%, in a static renewal test (daily renewal) (IIA 8.2/02). The study was carried out in accordance with OECD 203 with the exception that the concentration of the solvent was not reported. Nominal test concentrations were: 0.25, 0.50, 1.0, 2.0, 4.0 and 8.0 mg as/L, a control and a solvent control (DMF). Two replicates with 10 fish per concentration. 4 L test solution per vessel and each vessel was closed by caps. Observations: 5, 24, 48, 72 and 96 hours after test initiation.

Mean measured concentrations were 0.22, 0.43, 0.86, 1.7, 3.2 and 5.4 mg/L (68-88% of nominal). Measured test concentrations from freshly prepared test concentrations ranged from 77 – 101% of nominal and the measured test concentrations from the 24 h old solutions ranged from 52 – 92% of nominal. Fathead minnows in the 0.22 and 0.43 mg/L treatment groups appeared normal, with no treatment-related mortalities or overt signs of toxicity noted during the test. While no mortalities occurred in the 0.86 mg/L treatment group, all of the fish exhibited signs of toxicity by test termination. Percent mortality in the 1.7, 3.2 and 5.4 mg/L treatment groups at test termination was 80, 100 and 100%, respectively. Symptoms included surfacing, erratic swimming, lethargy, and loss of equilibrium.

24 hours LC_{50} of 2.3 mg as/L, 48-hours LC_{50} of 1.6 mg as/L, 72-hours LC_{50} of 1.4 mg as/L and 96-hours LC_{50} of 1.4 mg as/L (95% CL 0.86 – 1.7 mg as/L), based on mean measured test concentrations. All LC_{50} values were calculated using binomial probability method. Study is considered reliable and the endpoint is acceptable for classification.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

Twenty daphnids (*Daphnia magna*, ≤24 hours old) were exposed to a range of concentrations of 1,4-dimethylnaphthalene (batch H5510, purity 96.4%) (IIA 8.3.1/01) under flow-through conditions. The study was carried out in accordance with OECD 202. The study was conducted in two parts with the following nominal test concentrations: 0.16, 0.26, 0.43, 0.72, and 1.2 mg as/L (test 1) and 0.65, 1.1, 1.8, 3.0, and 5.0 mg as/L (test 2). Two replicates with 10 daphnids per treatment were carried out. Observations of immobility and abnormal behaviour of appearance were performed after 24 and 48 hours of exposure.
In the first test the mean measured test concentrations were 0.056, 0.10, 0.18, 0.31, and 0.48 mg as/L. Immobility occurred at concentrations of 0.18 mg/L and above. At the highest test concentration of 0.48 mg as/L, 15% immobilised daphnids were observed. Other symptoms included lethargy, erratic movement and paleness. All daphnids at the highest test concentration were pale and erratic. EC_{50} of the first test is reported to be > 0.48 mg as/L, based on mean measured test concentrations.
In the second test the measured test concentrations were 0.21, 0.33, 0.56, 0.94 and 2.2 mg as/L. Immobility was found at 0.33 mg as/L (5%) and increased dose-related to 100% at 2.2 mg as/L. The EC_{50} of the second test is calculated at 0.54 mg as/L (95% CL 0.33 – 0.94 mg as/L), based on mean measured test concentrations. Study is considered reliable and the endpoint is acceptable for classification.

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

See long-term aquatic hazard Section 11.6.3.

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

No additional data.

11.6 Long-term aquatic hazard

The long-term aquatic toxicity studies of 1,-4-dimethylnaphthalene were assessed in the Draft Assessment Report (October 2012) prepared in the context of the approval, under Reg. (EC) 1107/2009. Studies considered valid in the and DAR (reliability score of 1 or 2) have been included in this report. Other than the public literature data all studies were carried out under GLP and in accordance with OECD guidelines. Minor deviations were noted in one study but in general these did not affect the overall reliability of the studies. The deviations are included in the summaries were relevant. For the public literature studies the reliability of the studies were also assessed using Klimisch Scores.

Table 38: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test duration	Test material	Results[1]	Remarks	Reference
OECD 215	Rainbow trout (*Oncorhynchus mykiss*)	28 d	1,4-dimethylnaphtha-lene (lot number 14D03M01-02, purity 98.8%) Concentration: 0, 20, 46, 106, 243 and 560 µg a.s./L	NOECgrowth: 0.09 mg a.s./L Mean measured.	-	IIA 8.2/03, DocID 535A-105
Partly in accordance with early life stage test, OECD 210	*Gadus morhua*	4 d	1,4-dimethylnaphthalene, purity 98% Concentration: 0, 3.09, 2.92, 2.06, 1.03, 0.95 mg/L	NOEC <0.67 mg a.s./L Mean measured	Non GLP, public literature study. Klimisch score: 2 Mortality and sublethal effects were reported together therefore NOEC reflect mortality and sublethal effects together.	IIA 8.2/04
OECD 211	*Daphnia magna*	21 d	1,4-dimethylnaphthalene(batch 14D03M01-02, purity 98.8%)	NOEC: 0.16 mg a.s./L Mean measured.	-	IIA 8.3/02 DocID 535A-104

			Concentration: 25, 50, 100, 200 and 400 µg/L			
Partly in accordance with OECD 210	Sea urchin eggs (*Strongylocentrotus droebachiensis*)	4 d	1,4-dimethylnaphthalene, purity 98% Concentration: nominal conc. 2.92 and 0.95 mg as/L in the first test and 3.09, 2.06 and 1.03 mg as/L in the second test	NOEC: 0.54 mg a.s./L (test 1) and 0.31 mg/L (test 2) Mean measured.	Non GLP, public literature study. Klmisch score: 1	IIA 8.2/04
OECD 221	*Lemna gibba*	7 d	1,4-dimethylnaphthalene, batch 01C-01, purity 98.8% Concentration: 0.16, 0.31, 0.63, 1.3, 2.5 and 5.0 mg/L	NOEC 0.15 mg a.s./L Mean measured.	-	IIA 8.6/01 DocID 535A-103
OPPTS 850.5400, OECD 201, EEC C.3	*Pseudokirchneriella subcapitata*	96 h	1,4-dimethylnaphthalene, batch 01C-01, purity 98.8% Concentration: 0.028, 0.056, 0.11, 0.23, 0.45 and 0.90 mg a.s./L	72h NOEC 0.03 mg a.s./L Mean measured.	The validity criteria of OECD 201 were not met with respect to control growth.	IIA 8.4/01 DocID 535A-102

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

11.6.1 Chronic toxicity to fish

Rainbow trout were exposed to 1,4-dimethylnaphthalene under flow-through conditions. Nominal test concentrations of 1,4-dimethylnaphthalene (lot number 14D03M01-02, purity 98.8%) selected were control, solvent control (0.10 mL dimethylformamide/L), 20, 46, 106, 243 and 560 µg as/L (IIA 8.2/03). The study was carried out in accordance with OECD 215. Mean fish weight at test initiation was 1.1 g (range 1.0 – 1.3 g). Four replicates per treatment with 10 fish each.

Mean measured test concentrations, determined from samples of test water collected at test initiation and at approximately weekly intervals thereafter, were 18, 40, 90, 205 and 488 µg/L, which represented 90, 87, 85, 84 and 87% of nominal concentrations, respectively.

At test termination, there were no statistically significant differences ($p > 0.05$) in survival between treatment groups and the pooled control. Consequently, the NOEC for survival was 488 µg/L and the LOEC was > 488 µg/L. No significant differences between the negative and solvent control groups in growth rate. The differences between the pooled control and 205 and 488 µg/L, the two highest treatment groups, were statistically significant ($p \leq 0.05$). Consequently, the NOEC for growth rate was 90 µg/L and the LOEC was 205 µg/L. The NOEC was based on mean measured test concentration. Study is considered reliable and the endpoint is acceptable for classification.

In a non-GLP public literature study 1,4-dimethylnaphthalene, purity 98%, was added to seawater with fertilised Cod fish eggs (*Gadus morhua*) in a duplicate static test (IIA 8.2/04). The studies was partially in accordance with OECD 210 with the main difference being that mortality and sublethal effects were not reported separately. Approximately 50 cod eggs were placed in test beakers containing 100 ml of seawater mixed with the test substance. Two experiments were performed, the first test with concentrations at 2.92 and 0.95 mg/L and a control, the second at 3.09, 2.06 and 1.03 mg/L and a control. Observations of mortality and abnormal embryos were performed after 6 h, 1 day, 2 days and 4 days.

Analysed concentrations at t= 4 d in the first test were 1.75 and 0.54 mg/L, 60% and 57% of nominal, respectively (2.92 and 0.95 mg/L at t= 0h resp). Analysed concentrations at t= 4 d in the second test were and 1.08, 0.56 and 0.31 mg/L, 35%, 27% and 30%, respectively (3.09, 2.06 and 1.03 mg/L at t=0 h resp). At nominal concentrations of 2.92, 3.09 and 2.06 mg/L, the substance caused mortality or impairment of normal embryonic development. At 0.95 and 1.03 mg/L, a slight effect on development to the gastrula stage was observed. Therefore, the NOEC is lower than the lowest test concentration, which was 1.03 mg/L at t=0 h and 0.31 mg/L at t=4d. Mortality and sub-lethal effects are taken together in the results. Therefore, a NOEC based on mortality cannot be determined. A NOEC for mortality and sub-lethal effects together can be set at <0.67 mg/L, based on mean measured concentrations. Study is considered reliable (Klimisch Score 2) and the endpoint is acceptable for classification.

11.6.2 Chronic toxicity to aquatic invertebrates

In a *Daphnia magna* study daphnids (< 24-hours of age) were exposed during 21 days to a geometric series of five test concentrations 1,4-dimethylnaphthalene, a negative (dilution water) control and a solvent control (dimethylformamide 0.1 mL/L) under flow-through conditions (IIA 8.3/02). The study was carried out in accordance with OECD 211. Nominal test concentrations of 1,4-dimethylnaphthalene (lot number 14D03M01-02, purity 98.8%) selected for the test were 25, 50, 100, 200 and 400 µg/L. Two replicate test chambers were tested for each treatment and control. Each replicate contained two compartments with five daphnids, resulting in a total of 20 *Daphnia magna* in each treatment and control group. Test compartments were covered with Petri dish to minimise volatilisation. Daily observations of survival, clinical signs and reproduction. Body length and dry weight of surviving daphnids (F0) were measured.

Mean measured test concentrations were 24, 48, 89, 160 and 339 µg/L. Clinical effects of lethargy, discoloration and a smaller size of the daphnids were observed at 339 µg as/L.

NOEC for reproduction, length, and dry weight of the F0 generation is reported as 160 µg as/L. A 21-day EC_{50} for mortality is reported to be > 339 µg as/L and the 21-day EC_{50} for reproduction is 275 µg as/L (mean measured). An EC_{10} values were not reported. Study is considered reliable and the endpoint is acceptable for classification.

In a non-GLP public literature study 1,4-dimethylnaphthalene, purity 97.5%, was added to seawater with fertilised sea urchin eggs (*Strongylocentrotus droebachiensis*) in a duplicate static test (IIA 8.2/04). Nominal concentrations of 2.92 and 0.95 mg as/L in the first test and 3.09, 2.06 and 1.03 mg as/L in the second test. At fixed time intervals (6 h, 1 day, 2 days and 4 days) the number of abnormal and dead embryos noted. Test concentration was measured by ultraviolet spectrophotometry at test start and termination.

Mean measured concentrations were 1.75 and 0.54 mg/L, 60% and 57% of nominal, respectively, in the first test and 1.08, 0.56 and 0.31 mg/L, 35%, 27% and 30%, respectively, in the second test. In the first test, the no effect level was 0.54 mg/L (mean measured concentration. In the second test the no effect

level was 0.31 mg/L (mean measured concentration. Study is considered reliable and the endpoint is acceptable for classification.

11.6.3 Chronic toxicity to algae or other aquatic plants

The green alga, *Pseudokirchneriella subcapitata*, was exposed to a geometric series of six concentrations of 1,4-dimethylnaphthalene, batch 01C-01, purity 98.8%, a blank control and a solvent control (dimethylformamide 0.1 mL/L) under static conditions for 96 hours (IIA 8.4/01). The study was carried out in accordance with OECD 201. Twelve replicate test chambers were maintained in each treatment and control group. Nominal test concentrations selected were 0.028, 0.056, 0.11, 0.23, 0.45 and 0.90 mg/L. Initial cell density 5000 cells/mL. Cell densities were counted after 24, 48, 72 and 96 hours using and electronic particle counter.

Mean measured test concentrations over test duration were 0.030, 0.053, 0.11, 0.21, 0.44 and 0.86 mg as/L (95-107% of nominal). Cells appeared normal except at 0.86 mg as/L after 96 hours of exposure. Those cells were noted to be enlarged. Growth rate was inhibited by 3.6% at 0.053 mg as/L (significant) and was reduced with 77% at 0.86 mg as/L, the highest concentration, after 72 hours. Biomass was also significantly reduced at 0.053 mg as/L (8.7%) and further reduced by 95% at 0.86 mg as/L after 72 hours. Both reductions were dose-related. E_bC_{50} is reported as 0.32 mg as/L (95% CL: 0.30 – 0.35 mg as/L) and E_rC_{50} as 0.62 mg as/L (95% CL 0.60 – 0.64 mg as/L) after 72 hours of exposure. The E_bC_{50} and E_rC_{50} values after 96 hours were 0.33 and 0.60 mg as/L, respectively. EC_{10}s were not reported. NOE_bC and NOE_rC after 72 and 96 hours are both 0.030 mg as/L. All values based on mean measured test concentrations and compared with solvent control.

The validity criteria of OECD 201 (2001) are not met with respect to control growth. No exponential growth rate in the control. The mean variance of daily growth rate in the control was > 35% (mean value 79%). However, the study did meet the criteria of OECD 201 adopted July 1984 which was in effect at the time of the conduct of the study. In addition, due to volatility of the test substance and a desire to maintain test concentration throughout the study the test was done in a closed system. Due to the lack of gas exchange in this testing environment, algal growth is limited. The algae growth was exponential during the first 48 hours but quickly outgrew the carrying capacity of the media. Growth peaked very quickly so the algae were past logarithmic growth phase by 72 hours. Moreover, the observed effects of 1,4-DMN on green algal were evident and consistent at 48, 72 and 96 hours. These effects were observed during the early portion of the test when exponential growth was occurring as well as at 72 and 96-hours, after cell growth had peaked. The failure to have exponential growth between 48 and 72 hours did not appear to change the conclusion of the test. Study is considered reliable and the endpoint is acceptable for classification.

Fronds of duckweed, *Lemna gibba G3*, were exposed to six concentrations of 1,4-dimethylnaphthalene, batch 01C-01, purity 98.8%, a negative control (culture medium) and a solvent control (DMF 0.1 mL/L) under static-renewal conditions for seven days (IIA 8.4/01). The study was carried out in accordance with OECD 201. Nominal test concentrations selected were 0.16, 0.31, 0.63, 1.3, 2.5 and 5.0 mg/L. Three replicates for each test treatments and controls and one replicate without duckweed at the highest test concentration of 5.0 mg as/L. Renewal of test solutions on days 3 and 5 of the test. Four plants with in total 12 fronds were added to each replicate. Frond numbers were determined on days 3, 5 and 7. Observations of chlorosis, necrosis, break-up of duckweed colonies, death and any other abnormalities in plant or frond appearance were also performed on days 3, 5 and 7.

Mean measured test concentrations were 0.15, 0.31, 0.61, 1.2, 2.3 and 4.4 mg/L. Doubling time of frond number in the controls is about 3 days. Mean number of fronds after 7 days was 73 in the negative control and 75 in the solvent control and decreased treatment-related. Frond numbers after 7 days were 79, 67, 53, 35, 18, and 14 at 0.15, 0.31, 0.61, 1.2, 2.3, and 4.4 mg as/L. Percent inhibition increased from 8.6% to 81% at 0.31 to 4.4 mg as/L, at 0.15 mg as/L a stimulation of growth was noted of 6.8%. Frond numbers and percent inhibition were significant reduced at 0.31 mg as/L and onwards. Chlorotic

and necrotic fronds were observed at 0.31 mg as/L and onwards. 7-days I_rC_{50} for frond number is reported to be 1.1 mg as/L (95% CI 1.1 – 1.2 mg as/L), NOEC of 0.15 mg as/L both based on measured concentration. Study is considered reliable and the endpoint is acceptable for classification.

11.6.4 Chronic toxicity to other aquatic organisms

No additional data.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

The criteria for Category Acute 1 in line with Table 4.1.0 from the Guidance on the Application of the CLP Criteria are:

96 hr LC50 (for fish)	≤ 1 mg/l and/or
48 hr EC50 (for crustacea)	≤ 1 mg/l and/or
72 or 96 hr ErC50 (for algae or other aquatic plants)	≤ 1 mg/l.

The lowest LC_{50} in fish (Rainbow trout) was 0.67 mg/L. For aquatic invertebrates (*Daphnia magna*) the LC50 was 0.54 mg a.s./L. The 72 h E_rC_{50} in *Pseudokirchneriella subcapitata* was 0.62 mg a.s./L. Based on the observed LC_{50} values with the lowest LC50 value being 0.54 mg a.s./L 1,4-dimethylnaphthalene should be classified with Category Acute 1 with an M-factor of 1 (0.1 < L(EC)C50 < 1 mg/L).

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

In the OECD 301C ready biodegradability study 1,4-dimethylnaphthalene did fulfil the 60% criteria at the end of the study. The other available degradation data cannot confirm a rapid biodegradability. The substance is considered rapidly degradable (RD) according to the criteria outlined in section 4.1.2.9 of the CLP Regulation (EC) 1272/2008 where is indicated that the percentage degradation reached after 28 days in ready biodegradability tests may be used directly for the assessment of 'rapid degradability' if the data were derived with the MITI 1 test (OECD 301C). The criteria for Category Chronic 1, 2 and 3 the CLP Regulation (EC) 1272/2008 for rapidly degradable substances for which adequate chronic toxicity data are available are:

<u>Category Chronic 1:</u>

Chronic NOEC or ECx (for fish)	≤ 0.01 mg/l and/or
Chronic NOEC or ECx (for crustacea)	≤ 0.01 mg/l and/or
Chronic NOEC or ECx (for algae or other aquatic plants)	≤ 0.01 mg/l

<u>Category Chronic 2:</u>

Chronic NOEC or ECx (for fish)	≤ 0.1 mg/l and/or
Chronic NOEC or ECx (for crustacea)	≤ 0.1 mg/l and/or
Chronic NOEC or ECx (for algae or other aquatic plants)	≤ 0.1 mg/l

<u>Category Chronic 3:</u>

Chronic NOEC or ECx (for fish)	≤ 1 mg/l and/or
Chronic NOEC or ECx (for crustacea)	≤ 1 mg/l and/or
Chronic NOEC or ECx (for algae or other aquatic plants)	≤ 1 mg/l

Chronic toxicity studies are available for fish, invertebrates, algae and higher plants. The lowest chronic NOEC value in fish (Rainbow trout) was 0.09 mg a.s./L. For aquatic invertebrates (*Daphnia magna*) the lowest NOEC was 0.16 mg a.s./L. The lowest NOEC for aquatic plants (*Pseudokirchneriella subcapitata*) was 0.03 mg a.s./L. Based on the lowest NOEC of 0.03 mg a.s./L for *Pseudokirchneriella subcapitata* Category Chronic 2 applies according to Table 4.1.0 of the CLP Regulation (EC) 1272/2008 (RD and 0.01 < NOEC ≤ 0.1 mg/L).

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Acute (short-term) aquatic hazard: category Acute 1, M-factor: 1.

Long-term aquatic hazard: category Chronic 2.

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

No data.

12.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

No data.

12.1.2 Comparison with the CLP criteria

No data.

12.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

No data.

13 ADDITIONAL LABELLING

None.

14 REFERENCES

A full reference list of the available studies is included in Annex 1.

15 ANNEXES

The study summaries from the DAR of 1,4-dimethylnaphthalene have been included in Annex I.