Danish Ministry of the Environment
Environmental Protection Agency

Survey of 1,4-benzenediol, 2,5-bis(1,1-dimethyl ethyl)- (2,5-di-tert-butylhydroquinone)

Part of the LOUS-review

November 2012

Version for Public Consultation

Title:

Review and survey of
2,5-di-tert-butylhydroquinone

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Publisher:

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Year:

2012

ISBN no.

[xxxxxx]

Content

Preface

The Danish Environmental Protection Agency's List of Undesirable Substances (LOUS) is intended as a guide for enterprises. It indicates substances of specific concern due to the actual consumption in Denmark and for which the use should be reduced or eliminated completely. The first list was published in 1998 and updated versions have been published in 2000, 2004 and 2009. The latest version, LOUS 2009 [DEPA 2011] includes 40 chemical substances and groups of substances which have been classified as dangerous or which have been identified as problematic due to other concerns. The actual criteria employed by the Danish EPA for inclusion of substances in the list covers:

- Properties of concern according to the EU 'List of hazardous substances'
- Properties of concern identified using computer-based model calculations outlined in the Danish EPA's 'Advisory list for self-classification of dangerous substances' (the Self-classification list).
- PBT/vPvB substances as identified by the EU
- Substances on the EU 'Priority list of substances for further evaluation of their role in endocrine disruption'

Furthermore a tonnage threshold has been used. Substances used in quantities exceeding 100 tons per year in Denmark have been included in LOUS 2009. For substances which are the subject of special focus in Denmark, the tonnage threshold can however be different.

Over the period 2012-2015 all 40 substances and substance groups on LOUS will be surveyed. The surveys include collection of available information on the use and occurrence of the substances, internationally and in Denmark, information on environmental and health effects, on alternatives to the substances, on existing regulation, on monitoring and exposure and information regarding ongoing activities under REACH among others.

The Danish EPA will on the basis of the surveys assess the need for any further regulation, substitution/phase out, classification and labelling, improved waste management, development of new knowledge or increased dissemination of information.

This survey concerns 1,4-benzenediol, 2,5-bis(1,1-dimethylethyl)-. The reason for including the substance is the properties of concern according to the 'Advisory list for self-classification of dangerous substances': N;R50/53 [DEPA, 2011].

As the substance internationally is mostly known under the name of **2,5-di-tert-butylhydroquinone** this name will also be used for the substance in the rest of this report.

The preparation of this report has been supervised by a reference group consisting of:

Louise Grave Larsen, Danish Environmental Protection Agency (chairperson),
Lea Stine Tobiassen, Danish Environmental Protection Agency,
Ulla Hansen Telcs, Confederation of Danish Industries
Erik Hansen, COWI

Summary and conclusion

The knowledge available on 2,5-di-tert-butylhydroquinone is very limited.

The dominant use seems to be as anti-oxidant in various materials such as inks, paint and rubber. No precise information on other applications is available, but the substance may also be used as stabilizer in plastics. Based on data from the Danish Product Register the present gross consumption (inclusive export) of the substance in Denmark with preparations can be estimated to approximately 28 t/y and the net consumption to 3 t/y. No data, however, is available regarding import with articles, and the total consumption of the substance may well be significantly higher. The size of the consumption is, however, most likely not big enough to justify that the substance is included on LOUS.

The substance appears to be moderately acute toxic following ingestion and with the potential to cause dermal, eye (severe) and respiratory irritation. There are some indications of other effects on humans inclusive of impact on the immune system, skin sensitisation, and mutagenicity/ genotoxicity, but no solid documentation.

Regarding environmental fate and ecotoxicity QSAR and read-across indicate that the substance is not readily biodegradable and (very) toxic to aquatic organisms. The prediction of being (very) toxic to aquatic organisms is the reason why 2,5-di-tert-butylhydroquinone was listed on LOUS. This assessment is, however, not reflected in the self-classification undertaken by manufacturers and importers.

No studies regarding the fate of the substance during manufacture and use inclusive waste treatment and disposal are available. It is expected that the substance is largely destroyed by incineration processes and to the extent it is directed to landfills is strongly withheld within landfills and other depots.

No knowledge on alternatives is available.

Many important data gabs exist. These data gabs include:

- Detailed knowledge of applications and end-uses:
- Consumption by application area;
- Fate of the substance by handling of waste from manufacture and use activities as well as waste treatment processes;
- Alternatives available and advantages and drawbacks of alternatives;
- Solid documentation of human toxicity including long term effects, and
- Solid documentation of environmental fate and ecotoxicity.

Sammenfatning og konklusion

Den tilgængelige viden om 2,5-di-tert-butylhydroquinone er meget begrænset.

Den dominerende anvendelse er som antioxidant i forskellige materialer såsom blæk, maling og gummi. Ingen sikker viden om andre anvendelser er tilgængelig, men stoffet forventes også at blive anvendt som stabilisator i plastic. Baseret på data fra Produkt Registeret kan det nuværende bruttoforbrug (inklusiv eksport) af stoffet med materialer i Danmark estimeres til ca. 28 t/år og nettoforbruget til ca. 3t/y, men der er ingen data om importen med produkter og det totale forbrug kan sagtens være væsentligt større. Størrelsen af forbruget er dog sandsynligvis for beskedent til at retfærdiggøre at stoffet medtages på LOUS.

2,5-di-tert-butylhydroquinone er moderat akut giftigt i forbindelse med indtagelse og kan give hud-, øje- og indåndingsirritation. Der er tegn på andre effekter hos mennesker, herunder påvirkning af immunsystemet, hud overfølsomhed, og mutagenicitet/genotoxicitet, men der er ingen sikker dokumentation for disse effekter.

Med hensyn til skæbne i miljøet og økotoksicitet peger både QSAR beregninger og analogibetragtninger på, at stoffet ikke er let nedbrydeligt og (meget) giftigt overfor akvatiske organismer. Denne vurdering - at stoffet er (meget) giftigt overfor akvatiske organismer - var årsagen til at stoffet blev optaget på LOUS. Vurderingen er dog ikke bekræftet af vurderinger, der som led i selvklassifikation er foretaget af producenter og importører.

Der findes ingen viden om stoffets skæbne ved fremstilling og brug samt affaldsbehandling og bortskaffelse. Det forventes, at stoffet stort set destrueres ved forbrændingsprocesser og kun frigives i meget begrænset omfang fra lossepladser og andre depoter.

Der er ingen viden om alternativer.

Mange vigtige data mangler. Disse mangler omfatter:

- Detaljeret viden om anvendelser herunder slutanvendelser og forbrug for slutanvendelser.
- Viden om stoffets skæbne ved behandling af produktionsaffald og brugsaffald såvel som ved affaldsbehandlingsprocesser generelt.
- Viden om tilgængelige alternativer og fordele og ulemper ved disse.
- Studier af kroniske effekter og kræftfremkaldende egenskaber på langt sigt.
- Studier af reproduktions giftighed.
- Solide studier af giftighed overfor mennesker inklusive lang tids effekter.
- Solide studier af omsætning og giftighed i miljøet.

1. Introduction to the substance

1.1 Definition of the substance

2,5-di-tert-butylhydroquinone is a phenol derivative containing 2 phenol groups and 2 alkyl groups each consisting of three methyl groups.

CAS No: 88-58-4
EC No: 201-841-8

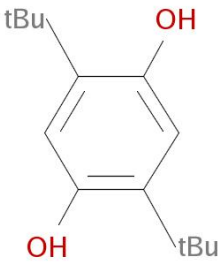
Relevant synonyms for 2,5-di-tert-butylhydroquinone includes:

- 1,4-benzenediol, 2,5-bis(1,1-dimethylethyl)-;
- 2,5-Di-tert-butyl-1,4-hydroquinone;
- 2,5-Bis(2-methyl-2-propanyl)-1,4-benzenediol;
- 1,4-Dihydroxy-2,5-di-*tert*-butylbenzene, and
- DTBHQ.

The substance is a cream or pale brown crystalline solid with the following physico-chemical properties [chemspider 2012; Chemical Book 2012]:

Molecular Formula:	$C_{14}H_{22}O_2$
Molecular weight:	222.33
Melting point:	215-219 ˚C
Boiling point:	321-324.52˚C
Solubility:	Almost insoluble in water
Flash point:	216˚C
Density:	1.07

Stability/storage: Stable. Incompatible with oxidizing agents. Can be stored at room temperature.



Source: http://esis.jrc.ec.europa.eu/

The substances is pre-registered and listed in the ESIS database. In ESIS it is indicated as a low-production-volume chemical.

TABLE 1
BASIC DATA FOR THE SUBSTANCE IN QUESTION

CAS No	EC No	Substance name	Pre-registered *1	Registered, tonnage band (t/y) *1	Danish Product register Tonnage, t/y *2	SPIN Tonnage, t/y *3
88-58-4	201-841-8	2,5-di-tert-butylhydroquinone	Yes	Not registered	27.7 (3)	11.8

*1 As indicated in the lists of pre-registered and registered substances at ECHA's website.

*2 Tonnage indicates the registered consumption and export in the Danish Product Register, June 2012. Data on consumption alone is stated in brackets. Detailed data on consumption in Denmark is presented in table 4.

*3 Included in the database of the Substances in Products In Nordic countries (SPIN) (http://188.183.47.4/DotNetNuke/default.aspx). The figure stated is the sum of consumption in 2010 registered for Denmark (3.4 t/y), Norway (0.4 t/y) and Sweden (7.0 t/y).

1.2 Function of the substance for main application areas

The dominant function of the substance is as an "antioxidant" in various materials including paint and lacquers, rubber, cosmetics and other products. It is also used as a stabilizer in plastics.

1.3 Data collection strategy

The existing knowledge published on the substance is scarce.

In this description of 2,5-di-tert-butylhydroquinone, the strategy has therefore been to rely on data obtained from Danish and international industry associations. Data collection has otherwise primarily been based on internet research utilizing home pages of EU institutions and international databases as well as consulting MSDS and SDS published by private companies.

2. Regulatory framework

2.1 Danish legislation

2.1.1 Existing legislation

The substance is not specifically addressed by any Danish legislation.

2.1.2 Non-legally binding activities

The substance is included on the DEPA List of Undesirable Substances (LOUS) [DEPA 2011].

2.2 REACH

No ongoing activities under REACH addressing 2,5-di-tert-butylhydroquinone have been identified. The substance is not included in any of the lists addressing chemicals of concern: the Community Rolling Action Plan (CoRAP) list of substances, the Candidate List or the Registry of Intentions.

Classification and labelling

2,5-di-tert-butylhydroquinone is not included in Annex VI to the CLP regulation (Regulation (EC) No 1272/2008); i.e. it does not have a harmonised classification.

Self-classification

The Classification & Labelling (C&L) Inventory database on the website of the European Chemicals Agency (ECHA) contains classification and labelling information on notified and registered substances received from manufacturers and importers. Companies have provided this information in their C&L notifications or registration dossiers. ECHA maintains the Inventory, but does not verify the accuracy of the information (ECHA, 2012).

Classification of 2,5-di-tert-butylhydroquinone listed in the database is shown in Table 2.

TABLE 2
CLASSIFICATION INFORMATION FROM CLP NOTIFICATIONS AND/OR REACH REGISTRATION DOSSIERS

CAS No	Hazard Class and Category Code(s) *1	Hazard Statement Codes *1	Number of notifiers
88-58-4	Acute tox. 4	H302	128 /155
	Skin irrit. 2	H315	108 /155
	Skin sens. 1	H317	48 /155
	Eye irrit. 2	H319	108 /155
	STOT SE 3	H335	76 /155
	Aquatic Chronic 2	H411	1 /155

1. Source : Classification and Labelling Inventory at http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database

- Acute toxicity category 4: H 302 Harmful if swallowed
- Skin irritation category 2: H 315 Causes skin irritation

- Skin sensitisation category 1: H317 May cause an allergic skin reaction
- Eye Irritation category 2: H319 Causes serious eye irritation
- Specific Target organ toxicity after single exposure category 3 (STOT SE 3) H335: May cause respiratory irritation:
- Aquatic Chronic 2: H411 Toxic to aquatic life with long lasting effects.

2.3 International agreements

The substance is not specifically addressed by any international agreement.

2.4 Eco-labels

The substance is not directly covered by any existing eco-label.

TABLE 3
ECO-LABELS TARGETING 2,5-DI-TERT-BUTYLHYDROQUINONE

Eco-label	Mixtures and articles
Nordic Swan	Not covered by existing eco-labels
EU Flower	Not covered by existing eco-labels
German Blue Angel	Not covered by existing eco-labels

3. Manufacture and uses

3.1 Global manufacture and use of 2,5-di-tert-butylhydroquinone

Several suppliers of the substance are present internationally, but no data on global production and consumption divided into applications are available.

The substance is included in the list by the US Food and Drug Administration on indirect additives used in food contact and may be used as an adhesive or component in paper and cardboard or in manufacturing of certain polymers. In the U.S. Code of Federal Regulations Title 21 (Food and Drugs), the substance is mentioned in the following sections [CFR 2012]:

Sec. 175.105: Adhesives - no restrictions.
Sec. 176.170: Components of paper and paperboard in contact with aqueous and fatty foods: For use only as an antioxidant for fatty based coating adjuvants provided it is used at a level not to exceed 0.005% by weight of coating solids.
Sec. 176.180: Components of paper and paperboard in contact with dry food - no restrictions.
Sec. 176.210: Defoaming agents used in the manufacture of paper and paperboard - no restrictions.
Sec. 177.2260: Filters, resin-bonded. 2,5-Di-*tert* -butyl hydroquinone for use only in lubricant formulations for rayon fiber finishing and at a usage level not to exceed 0.1 percent by weight of the lubricant formulations.
Sec. 177.2420: Polyester resins, cross-linked. Total amount of inhibitors (inclusive 2,5-di-tert-butylhydroquinone) not to exceed 0.08 percent by weight of finished resin.
Sec. 177.2800 Textiles and textile fibers - no restriction.

3.2 Manufacture and use of 2,5-di-tert-butylhydroquinone in the EU

It is not known, whether the substance is produced within the EU.

The substance is included in the EU list of substances used in cosmetic products [1] . The indicated function is “Antioxidant”. The INCI name of the substance is di-t-butylhydroquinone.

The European Council of producers and importers of paints, printing inks and artists' colours (CEPE) informs that the substance is used as an antioxidant in anti-fouling paints. According to CEPE other known uses include [CEPE 2012]:

- Low level impurity in mono-t-butyl hydroquinone used as an antioxidant in printing inks;
- Low level impurity (<0.2%) in some UV additives and resale antioxidant spray used by printers to keep offset ink 'fresh' in the duct of the presses overnight or during job changes;
- Use (0.5-1.0%) in the binder/resin of the UV metallic inks, and
- Use in pigment concentrates (small amount).

[1] 2006/257/EC: Commission Decision of 9 February 2006 amending Decision 96/335/EC establishing an inventory and a common nomenclature of ingredients employed in cosmetic products (Text with EEA relevance)

A Material Safety Data Sheet (MSDS) describes the uses as follows: Polymerisation inhibitor, anti-oxidant, stabiliser against UV deterioration of rubber.

Other uses indicated by SDSs include reagent, laboratory chemical and manufacture of substances.

Information has been requested from the European Chemical Industry Council (CEFIC) and the European Plastic Converters (EuPC) but no response has been received.

As the substance is not included in the database of registered substances under REACH, no data on the use is available from registrations.

3.2.1 Statistics on manufacture and import/export of 2,5-di-tert-butylhydroquinone on its own

No separate commodity or activity codes exist for the substance in the statistics from Eurostat. Therefore it is not possible to obtain statistical information regarding manufacture, import and export of the substance for the EU27.

3.3 Manufacture and use of 2,5-di-tert-butylhydroquinone in Denmark

3.3.1 Manufacture, import, export and consumption of 2,5-di-tert-butylhydroquinone on its own

No separate commodity codes exist for the substance in the statistics from Statistics Denmark. Therefore it is not possible to obtain statistical information regarding manufacture, import and export of the substance for Denmark.

No information indicates that the substance is manufactured in Denmark.

3.3.2 Import, export and consumption of 2,5-di-tert-butylhydroquinone in preparations

The Danish Association for Plastic Industries (Plastindustrien) informs that the substance is known as an additive in production of plastics. The function is defined as stabilizer. However, more comprehensive data regarding actual applications and consumption in Denmark are not available [Plastindustrien 2012].

The Danish Coatings and Adhesives Association (DFL) confirms the use described by CEPE as anti-oxidant in anti-fouling paints. No information has been available regarding the use in printing inks [DFL 2012].

Data on 2,5-di-tert-butylhydroquinone in preparations registered in the Danish Product Register are summarised in TabLe 4.

The Danish Product Register includes information from notification of substances and mixtures used occupationally and which contain at least one substance classified as dangerous in a concentration of at least 0.1% or 1% (depending on the classification of the substance). The notification duty applies to companies that produce, import or change the trade name of hazardous chemical products in quantities exceeding 100 kg per year. As 2,5-di-tert-butylhydroquinone does not have a harmonised classification the registration must only occur, if it is a constituent of products, which are classified as dangerous due to the presence of other constituents. The data consequently do not

provide a complete picture of the presence of the substance in mixtures placed on the Danish market. The amounts registered are for occupational use only.

Aside from the consumption in preparations placed on the Danish market approx. 25 tonnes of the substance is exported in preparations (confidential).

No data is available regarding import of the substance to Denmark incorporated into articles. Import with articles may well be responsible for consumption in Denmark significantly higher than the 3 t/y stated in Table 4.

TABLE 4
2,5-DI-TERT-BUTYLHYDROQUINONE IN PREPARATIONS PLACED ON THE DANISH MARKET IN 2011 AS REGISTERED IN THE DANISH PRODUCT REGISTER

Use area	tonnes/year
Biocides	0.1-1.0
Paint and lacquers	1.0-2.0
Other applications	0.1-1.0
Total (rounded average)	3

3.3.3 Import, export and consumption of 2,5-di-tert-butylhydroquinone in articles

No data is available.

3.3.4 Summary on the use of 2,5-di-tert-butylhydroquinone in Denmark

The dominant use seems to be as an anti-oxidant in various materials such as plastic, paint, rubber, etc. No precise information on other applications is available. Based on data from the Danish Product Register the consumption of the substance in Denmark as a componentof preparations can be estimated as approximately 3 t/y. Including import with articles the total consumption may well be significantly higher.

4. Waste management

4.1 Waste from manufacture and use of 2,5-di-tert-butylhydroquinone

No studies regarding the fate of the substance by handling of waste from manufacture and use of the substance are available. The fate of the substance depends strongly on how the waste is collected and treated.

In Denmark manufacturing waste is collected and treated as organic chemical waste, in which case the waste is incinerated and the substance is most likely completely destroyed.

4.2 Waste products from the use of 2,5-di-tert-butylhydroquinone in mixtures and articles incl. recycling

No studies are available regarding the fate of the substance through handling of waste articles and mixtures containing the substance. The fate of the substance depends strongly on how the waste is collected and treated. As no exact knowledge on this issue is available it is not possible to assess the fate of the substance. No information on recycling is available.

4.3 Releases of 2,5-di-tert-butylhydroquinone from waste disposal

No studies regarding the fate of the substance during waste disposal are available. The fate is therefore assessed as follows:

As a combustible organic substance with low water solubility that solely or dominantly is used in combustible materials 2,5-di-tert-butylhydroquinone should be expected to:

Be largely destroyed by incineration processes - it is however possible that small quantities are released to air or with air gas cleaning products or clinker directed to landfills or other depots.

Be strongly withheld within landfills and other depots - it is however possible that small quantities are released to water recipients with emission of leachate.

In waste water to be precipitated as sewage sludge to be incinerated, landfilled or used for land application - it is, however, possible that small quantities are released to water recipients with treated waste water.

The knowledge available does not allow any prediction of the fate of the substance by biological processes such as composting. However, at stated in section 6, the substance is probably not readily biodegradable.

5. Environmental effects and fate

The information identified and used for this section is the following:

- The Danish EPA QSAR database OASIS;
- The self classifications obtained from the REACH Classification & Labelling inventory (C&L inventory), and
- A number of (Material) Safety Data Sheets ((M)SDSs) identified (see reference list)

No (peer-reviewed) articles have been identified.

5.1 Classification and Labelling

TABLE 5
C&L INVENTORY HAZARD STATEMENT CODES FOR ENVIRONMENTAL EFFECTS

CAS No	Hazard Class and Category Code(s)	Hazard State-ment Codes	Number of notifiers *1
88-58-4	Aquatic Chronic 2	H411	1 / 155

1. Indicates the number of notifiers suggesting the hazard statement code, and the total number of notifiers.

- Aquatic Chronic 2: H411 Toxic to aquatic life with long lasting effects.

5.1.1 Danish Advisory list for Self-Classification

The Danish Advisory list for Self-Classification, which is based on the Danish EPA QSAR database predictions has identified 2,5-di-tert-butylhydroquinone (1,4 benzenediol, 2,5-bis(1,1-dimeyhylethyl)-) for classification as [DEPA 2009]:

- Aquatic Chronic category 1: H410 Very toxic to aquatic life with long lasting effects (N, R50/53).

This classification has triggered the listing of 2,5-di-tert-butylhydroquinone (1,4 benzenediol, 2,5-bis(1,1-dimeyhylethyl)-) on the List of Undesirable Substances (LOUS), 2009.

5.2 Fate in the environment

No original test data have been identified and most of the identified (M)SDSs indicate that there are no data.

5.2.1 Persistence

One MSDS indicates that the substance is highly persistent without indicating a reference. One out of 155 C&L inventory entries classifies the substance as H411 Toxic to aquatic life with long lasting effects (aquatic chronic category 2) and the Danish EPA QSAR database OASIS suggests H410 Very

toxic to aquatic life with long lasting effects (Aquatic chronic category 1), the latter based on indications that primary and ultimate degradation may take weeks to months.

5.2.2 Bioaccumulation

One MSDS indicates that the substance has a low bioaccumulation potential, but no reference is given. The estimations in the Danish EPA QSAR database OASIS indicates moderate bioaccumulation potential (Log Pow = 4.85) and probably not readily biodegradable.

5.3 Environmental effects

The only test data identified are three Microtox (bacteria) tests reported in a MSDS:

- EC50 = 3.86 mg/L (15 min)
- EC 50 = 4.25 mg/L (5 min)
- EC 50 = 4.65 mg/L (30 min))

No original reference for the test results is given in the MSDS.

One MSDS indicates that the substance is very toxic to organisms. This conclusion seems to be based on read-across and grouping considerations.

The Danish EPA QSAR database OASIS [Oasis 2010] predicts fathead minnow as the most sensitive organism, with an LC_{50} of 0.64 mg/L triggering the proposed classification as very toxic to the aquatic environment.

5.4 Summary

Very little information about the environmental fate and ecotoxicity of the substance has been identified and current predictions of environmental fate & behaviour and ecotoxicity is purely/mainly based on QSAR and read-across, which indicate that the substance is not readily biodegradable and (very) toxic to aquatic organisms. This, however, is only reflected in 1/155 entries in the REACH C&L inventory (Aquatic Chronic 2) and in the classification proposed by the DEPA QSAR database OASIS (Aquatic Chronic 1). Therefore, although we do not have the evidence behind the self classifications in the C&L inventory, lack of classification as dangerous in almost all of those entries *seems* to be based on lack of experimental data with little/no consideration of QSAR predictions. The only self-classification recognising the substance as dangerous may be based on the Microtox data since only Aquatic Chronic 2 is proposed. Until further experimental data is available, the classification should rely on the QSAR prediction of aquatic toxicity.

6. Human health effects

The information identified and used for this section is the following:

- The Danish EPA QSAR database OASIS;
- The self classifications obtained from the REACH Classification & Labelling inventory (C&L inventory);
- A number of (Material) Safety Data Sheets ((M)SDSs)(see reference list), and
- A number of (peer-reviewed) articles identified (only abstracts have been screened within the scope of this project).

6.1 Classification and Labelling

TABLE 6
C&L INVENTORY HAZARD STATEMENT CODES FOR HUMAN HEALTH EFFECTS

CAS No	Hazard Class and Category Code(s)	Hazard State-ment Codes	Number of notifiers *1
88-58-4	Acute tox. 4	H302	128 / 155
	Skin irrit. 2	H315	108 / 155
	Skin sens. 1	H317	48 / 155
	Eye irrit. 2	H319	108 / 155
	STOT SE 3	H335	76 / 155

1 Indicates the number of notifiers suggesting the hazard statement code, and the total number of notifiers.

- Acute toxicity category 4: H 302 Harmful if swallowed
- Skin irritation category 2: H 315 Causes skin irritation
- Skin sensitisation category 1: H317 May cause an allergic skin reaction
- Eye Irritation category 2: H319 Causes serious eye irritation
- Specific Target organ toxicity after single exposure category 3 (STOT SE 3) H335: May cause respiratory irritation

6.1.1 Danish Advisory list for Self-Classification

The Danish Advisory list for Self-Classification, which is based on the Danish EPA QSAR database predictions has identified 2,5-di-tert-butylhydroquinone (1,4 benzenediol, 2,5-bis(1,1-dimeyhylethyl)-) ether for classification as [DEPA 2009]:

- Acute toxicity Category 4: H 302 Harmful if swallowed (Xn; R22)
- Skin irritation 2: H 315 Causes skin irritation (Xi; R 38)

6.2 Mechanisms

2,5-di-tert-butylhydroquinone is an antoxidant and a calcium ATPase inhibitor, i.e. inhibiting the enzyme sarco/endoplasmic reticulum ATPase and thereby the Ca++ uptake [Paula et al., 2009; Kabbara and Stephenson DG, 1997] and when used intracellularly, increases the intracellular CA++ level, e.g. in sperm [Perry et al., 1997].

6.3 Biokinetics - ADME

No specific information is found on the biokinetics of 2,5-di-tert-butylhydroquinone.

6.4 Acute toxicity

2,5-di-tert-butylhydroquinone is moderately toxic following oral exposure with reported LD_{50} values for mouse and rat in the range of 800-1000 mg/kg [RTECS 2012]. This triggers the classification H302: Harmful if swallowed (acute oral toxicity category 4), which is a consistent self classification in the C&L inventory (128/155) and in the investigated (M)SDSs. This is also in line with the DEPA QSAR prediction [OASIS 2010].

A Safety Data Sheet reports a dermal LD50 > 21,000 mg/kg in guinea pigs without indicating the reference. No other dermal toxicity data have been identified.

6.5 Skin, eye and respiratory irritation

In the identified (M)SDSs and in the majority of the C&L inventory entries (108/128), the substance is classified as a skin and eye irritant (category 2):

- H315: Causes skin irritation (also identified in Danish EPA QSAR prediction [DEPA 2009]).
- H319: Causes serious eye irritation.

The original studies behind these classifications have not been identified, but a (M)SDS indicates:

- Skin irritation: Rabbit, 24 hours, slight to moderate.
- Eye irritation: Rabbit, strong.

Some of the identified (M)SDSs and 76/155 entries in the C&L inventory classify the substance as a respiratory irritant (H335 May cause respiratory irritation). Non-allergic asthma-like symptoms are mentioned as a result of exposure to high levels of the compound in one MSDS.

6.6 Immunotoxicity/Sensitisation

There are some indications that 2,5-di-tert-butylhydroquinone may interfere with the immune system. The Ca++ signal mechanisms seem to be needed, but are not sufficient for affecting histamine secretion and degranulation in RBL-2H3 cells [Kitajima et al., 1995 and Akasaka et al., 1996]. Also the release of Interleukin-4 (IL-4) and monocyte chemotactic protein-1 (MCP-1) production is affected by 2,5-di-tert-butylhydroquinone in a dose-dependent manner [Onos e et al., 1998]. IL-4 is involved in the development of allegic responses through induction of T helper cells and promotion of IgE production and is therefore associated with allergies.

48/155 C&L inventory entries classify for skin sensitisation (H317 May cause an allergic skin reaction). None of the identified (M)SDSs classify for this endpoint. One (M)SDS cites a guinea pig study indicating that 2,5-di-tert-butylhydroquinone is not a skin sensitizer; however no precise reference is given.

6.7 Repeat dose, target organ

No repeat dose toxicity studies have been identified, except the studies referred to under carcinogenicity below.

6.8 Mutagenicity/carcinogenicity

2,5-di-tert-butylhydroquinone has been shown to be capable of causing DNA cleavage in a supercoiled plasmid DNA, pUC18 *in vitro* test system, although not as efficiently as tert-butylhydroquinone (TBHQ) [Okubo et al., 1997]. Oxidative DNA damage of 2,5-di-tert-butylhydroquinone was also evaluated in a test system measuring the formation of 8-hydroxydeoxyguanosine (8OHdG) in calf thymus DNA. 2,5-di-tert-butylhydroquinone induced the formation of 8OHdG and its effect was stimulated by CuCl2. Also in this study 2,5-di-tert-butylhydroquinone was much more potent than TBHQ [Nagai et al., 1996]. Further, 2,5-di-tert-butylhydroquinone results in increased expression of GSTP1 protein, which may play a role in susceptibility to cancer [CDT 2012]. As above, 2,5-di-tert-butylhydroquinone seems to be less potent than TBHQ. Finally, the DEPA QSAR predictions [OASIS-2012] for this endpoint are largely negative with only a few positives.

2,5-di-tert-butylhydroquinone has been tested in a 24 week oral (1% in diet) study in Syrian male hamsters showing forestomach papillomas [Lam and Gard, 1991] and in an oral gavage (1 mg in 0.2 ml corn oil per week in four weeks) study in female ICR mice showing no significant tumour formation in the forestomach [Wattenberg et al., 1980].

No C&L entries or identified (M)SDSs have classified 2,5-di-tert-butylhydroquinone for this endpoint.

6.9 Summary

2,5-di-tert-butylhydroquinone is not extensively tested for human toxicity. In particular, there seems to be a lack of long-term testing.

Based on the available information 2,5-di-tert-butylhydroquinone appears to be moderately acute ly toxic following ingestion with the potential to cause dermal, eye (severe) and respiratory irritation.

There are some indications that 2,5-di-tert-butylhydroquinone may interfere with the immune system. 48/155 C&L inventory self-classifications classify for skin sensitisation. One SDS cites a guinea pig study to indicate that 2,5-di-tert-butylhydroquinone is not a skin sensitizer; however no precise reference is given.

There are some indications that 2,5-di-tert-butylhydroquinone may be mutagenic/genotoxic, although consistently less potent than the structurally related tert-butylhydroquinone (TBHQ). However, testing has not been performed according to regulatory testing schemes/batteries. A 24 week hamster diet study indicates that 2,5-di-tert-butylhydroquinone may cause tumour formation in the forestomach. No C&L entries or identified (M)SDSs have classified 2,5-di-tert-butylhydroquinone for this endpoint.

7. Monitoring data and exposure

7.1 Monitoring of 2,5-di-tert-butylhydroquinone in the environment and releases from point sources

2,5-di-tert-butylhydroquinone is so far not included in the National Monitoring and Assessment Programme for the Aquatic and Terrestical Environment (NOVANA) in Denmark, and no data are available regarding monitoring of 2,5-di-tert-butylhydroquinone in the environment and releases from point sources.

TABLE 7
2,5-DI-TERT-BUTYLHYDROQUINONE INCLUDED IN THE NATIONAL MONITORING AND ASSESSMENT PROGRAMME FOR THE AQUATIC AND TERRESTRIAL ENVIRONMENT, NOVANA 2011-2015

Substance	Point sources	Streams	etc.
88-58-4	Not included	Not included	Not included

TABLE 8
MOST RECENT MONITORING DATA FOR 2,5-DI-TERT-BUTYLHYDROQUINONE IN THE ENVIRONMENT FROM THE NATIONAL NOVANA PROGRAMME

Substance	Medium	Number of samples	Median (maximum) concentration, mg/kg dw	PNEC value mg/kg dw	Year	Source
88-58-4			No data			

7.2 Human exposure and biomonitoring

7.2.1 Intake of 2,5-di-tert-butylhydroquinone

No data are available.

7.2.2 Human biomonitoring data

No data are available.

TABLE 9
BIOMONITORING DATA OF 2,5-DI-TERT-BUTYLHYDROQUINONE.

Population group	Specimen	Median concentration µg/L	Number of samples	Country	Year	Data source

No data

8. Information on alternatives

CEPE informs that no alternatives are available regarding the use of the substance in paint without affecting the performance of the paint [CEPE 2012]. No alternatives in this context have actually been identified.

No information regarding alternatives for other uses is available.

9. Abbreviations and acronyms

CAS	Chemical Abstracts Service
CEFIC	European Chemical Industry Council
CEPE	The European Council of producers and importers of paints, printing inks and artists' colours.
CLP	Classification, labelling and packaging of substances and mixtures (EU regulation)
C&L	Classification and labelling
CN8	Statistical classification system (commodity statistics)
CoRAP	Community Rolling Action Plan
DEPA	Danish Environmental Protection Agency
DFL	Danish Coatings and Adhesives Association
DNA	Deoxyribonucleic acid
EC	European Community
ECHA	European Chemicals Agency
EEC	European Economic Community
ESIS	ESIS (European chemical Substances information System)
EPA	Environmental Protection Agency
EU	European Union
EU27	European Union med 27 member states
EuPC	European Plastics Converters
FEICA	The Association of the European Adhesive and Sealant Industry
IUCLID	International Uniform Chemical Information Database
Log Pow	Octanol–water partition coefficient
LOUS	List of undesirable substances
MSDS	Material Safety Data Sheet
NOVANA	Danish National Monitoring and Assessment Programme for the Aquatic and errestrial Environment
OECD	The Organisation for Economic Co-operation and Development
QSAR	Quantitative Structure–Activity Relationship
PBT	Persistent bioaccumulative toxic (chemical)
REACH	REACH is the European Community Regulation on chemicals and their safe use. It deals with the **R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emical substances
SDS	Safety Data Sheet
SVHC	Substances of Very High Concern
TBHQ	Tert-butylhydroquinone
UV	Ultra Violet (light)
vPvB	very Persistent very Bioaccumulative (chemical)

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