Danish Ministry of the Environment
Environmental Protection Agency

Survey of 1,6-hexandioldi-glycidylether

Part of the LOUS-review

November 2012

Version for Public Consultation

Title:

Review and survey of
1,6-hexandiol diglycidyl ether

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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 either been classified as dangerous or identified as problematic due to other concerns. The criteria employed by the Danish EPA for inclusion of substances on the list include:

- 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 and fulfilling any of the abovementioned criteria 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 1,6- hexandiol diglycidyl ether . The reason for including the substance is the following properties of concern in relation to the 'Advisory List for Self-classification of Dangerous Substances': Carc3;R40 [DEPA 2011].

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

Lea Stine Tobiassen, Danish Environmental Protection Agency (chairperson),
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Summary and conclusion

The knowledge available on 1,6-hexandiol diglycidyl ether is rather limited.

The dominant use of 1,6-hexandiol diglycidyl ether is as a reactive dilutant in epoxy systems. A dilutant is an organic liquid added to resin formulations, with no solvent power, to reduce viscosity and to ease flow movement or to improve the consistency and applicability These epoxy systems may have many different end uses. No certain information on other applications is available.

The consumption of 1,6-hexandiol diglycidyl ether in Denmark registered in the Danish Product Register has over the past 5 years declined from over 100 t/y to a gross consumption (inclusive export) of about 55 t/y and a net consumption of about 43 t/y . However, as not all mixtures containing 1,6-hexandiol diglycidyl ether are registered in the Danish Product Register, it is estimated that the total consumption in Denmark may potentially still be about 100 t/y or even above.

It is known that the substance is a skin and eye irritant, and a skin sensitizer. QSAR estimates indicate that the substance is a suspected carcinogen. This prediction is the reason why 1,6-hexandiol diglycidyl ether was listed on LOUS. The scarce data available do not support this QSAR indication.

The substance is, furthermore, classified by Self- Classifications for aquatic chronic toxicity (Category 3: H412 Harmful to aquatic life with long lasting effects). Other serious consequences of continued use of 1,6-hexandiol diglycidyl ether have not been identified and documented.

Use and disposal of hardened epoxy systems are not likely to cause significant release of 1,6-hexandiol diglycidyl ether although no studies that could confirm this assessment have actually been carried out. Disposal of unhardened residues at landfills may cause release of the substance with leachate potentially leading to emission of the substance to water environments. The available know-ledge does not allow for any prediction of the fate of the substance by biological processes such as waste water treatment.

No monitoring data on exposure of the substance to humans or the environment are available.

Alternatives to this substance exist. At least one of the alternatives presented (C12-14 glycidylether) seems to be less irritating and less toxic than 1,6-hexandiol diglycidyl ether. However, it is not known whether this alternative is appropriate for all applications. Industry associations claim that substitution of 1,6-hexandiol diglycidyl ether may cause problems related to e.g. quality and costs.

Many important data gaps exist. These data gaps include:

- Detailed knowledge of applications inclusive end-uses;
- Consumption by application areas;
- Fate of the substance by handling of waste from manufacture and use activities as well as waste treatment processes;
- Studies on chronic effects and long-term carcinogenicity;
- Studies on reproductive toxicity;
- Conclusive dermal absorption studies, and
- Long-term aquatic and terrestrial toxicity studies.

Sammenfatning og konklusion

Den tilgængelige viden om 1,6-hexandioldiglycidylether er meget begrænset. Den dominerende anvendelse af 1,6-hexandioldiglycidylether er som reaktiv fortynder i epoxy systemer. En fortynder er en væske som kan blandes med tyktflydende opløsninger af polymerer o.lign. uden virke opløsende på bindemidlet. Formålet er at reducere viskositeten og forbedre konsistensen og brugsegenskaberne (flyder bedre ud). Disse epoxy systemer har mange forskellige anvendelser. Der er ingen sikker viden om andre anvendelser.

Forbruget af 1,6-hexandioldiglycidylether i Danmark registeret i Produkt Registeret er i løbet af de sidste 5 år mindsket fra mere end 100 t/år til et bruttoforbrug (inklusive eksport) på ca. 55 t/y og et nettoforbrug på ca. 43 t/y. Da alle produkter, som indeholder 1,6-hexandioldiglycidylether, imidlertid ikke er registeret i Produkt Registeret, er det vurderet, at totalforbruget i Danmark stadigvæk sagtens kan være af størrelsen 100 t/y eller måske større.

Det vides at 1,6-hexandioldiglycidylether forårsager irritation af hud og øjne og kan gore huden følsom for allergi. QSAR estimater peger på at stoffet må mistænkes for at være kræftfremkaldende. Denne vurdering var årsagen til at 1,6-hexandioldiglycidylether blev optaget på LOUS. De få data, der er tilgængelige, støtter dog ikke denne QSAR vurdering.

Stoffet er tillige ved selvklassificering foretaget af virksomheder vurderet at have kroniske giftvirkning i det akvatiske miljø (Aquatic chronic tox. 3: H412 Skadelig for vandlevende organismer, med langvarige virkninger). Herudover er ikke identificeret og dokumenteret alvorlige konsekvenser af forsat brug af 1,6-hexandioldiglycidylether.

Brug og bortskaffelse af hærdet epoxy vurderes næppe at medføre væsentlig frigivelse af 1,6-hexandioldiglycidylether. Der er dog ikke udført undersøgelser, der kunne bekræfte denne antagelse. Bortskaffelse af uhærdede rester til lossepladser kan forårsage frigivelse af stoffet med perkolat som potentielt kan være en kilde til eksponering af vandmiljøet. Det er dog ikke muligt ud fra den foreliggende viden at forudsige stoffets skæbne ved biologiske processer såsom spildevandsrensning. Ingen undersøgelsesdata om den faktiske påvirkning af mennesker og miljø med stoffet er tilgængelige.

Der findes alternativer til 1,6-hexandioldiglycidylether. Mindst et af de præsenterede alternativer(C12-14 glycidylether) synes at være mindre irriterende og giftigt end 1,6-hexandioldiglycidylether. Det vides dog ikke om dette alternativ er brugbart til alle anvendelser. Industri organisationer hævder, at substitution af 1,6-hexandioldiglycidylether vil give problemer knyttet til fx kvalitet og omkostninger.

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.
- Studier af kroniske effekter og kræftfremkaldende egenskaber på langt sigt.

- Studier af reproduktions giftighed.
- Solide studier af hudoptag.
- Studier af giftighed på langt sigt i både vand- og jordmiljøer.

1. Introduction to the substance

1.1 Definition of the substance

1,6-hexandiol diglycidyl ether is an ether compound connected to ethylene oxide (oxirane) at both ends.

CAS No: 16096-31-4
EC No: 240-260-4

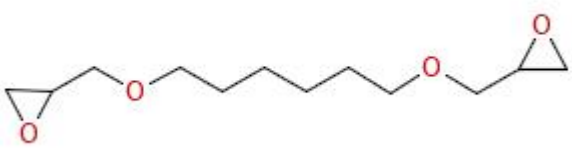
Relevant synonyms for 1,6-hexandiol diglycidyl ether include:

- hexane,1,6-bis(2,3-epoxypropoxy);
- 1,6-bis(2,3-epoxypropoxy)hexane;
- 1,6-bis(glycidyloxy)hexane;
- 1,6-hexamethylenediol diglycidyl ether;
- hexamethylene diglycidyl ether;
- hexamethylene glycol diglycidyl ether;
- hexanediol diglycidyl ether, and
- HDDGE.

The substance is a colourless and odourless liquid at room temperature and standard atmospheric pressure with the following physico-chemical properties [Lookchem 2012; World of chemicals 2012; yg-chem 2012]:

Molecular Formula:	$C_{12}H_{22}O_4$
Molecular weight:	230.3
Melting point:	71˚C [OASIS 2010]
Boiling point:	328,7˚C
Solubility:	Insoluble in water/soluble in organic solvents
Flash point:	120-179˚C
Density:	1.076 g/cm^3
Log Pow:	0.84 [OASIS 2010]
Vapour pressure:	0.002 mg Hg (very little volatile) [OASIS 2010]

Structural formula according to registration:



TABEL 1 BASIC DATA FOR THE SUBSTANCE IN QUESTION

CAS No	EC No	Substance name	Pre-registered *1	Registered, tonnage band (t/y) *1
16096-31-4	240-260-4	1,6-bis(2,3-epoxypropoxy)hexane	Yes	1,000-10,000

*1 As indicated in the lists of preregistered and registered substances at ECHA's website. For each separate registration the registered tonnage is indicated.

1.2 Function of the substance for main application areas

The dominant function of the substance is as a reactive dilutant, in particular related to epoxy systems. A dilutant is an organic liquid added to resin formulations, with no solvent power, to reduce viscosity and to ease flow movement or to improve consistency and applicability.

1.3 Data collection strategy

The existing knowledge published on the substance is very scarce.

The strategy has therefore been to rely on data obtained from Danish and international industry associations in this description of 1,6-hexandiol diglycidyl ether. Data collection has otherwise primarily been based on internet searching 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

1,6-hexandiol diglycidyl ether is not specifically addressed by any Danish legislation.

2.1.2 Non-legally binding activities

The substance is included on the Danish EPA **L**ist **o**f **U**ndesirable **S**ubstances (LOUS) [DEPA 2011] which aims at encourage reducing and phasing out of the substance. Also, the Danish Advisory List for Self-Classification of Dangerous Substances proposes that the substance should be considered for classification as a potential carcinogen, if no test data exist [DEPA 2009].

2.2 EU legislation

2.2.1 REACH

1,6-hexandiol diglycidyl ether is registered under REACH in the span 1,000 - 10,000 t/y and a Chemical Safety Report (CSR) is available.

No ongoing activities under REACH addressing 1,6-hexandiol diglycidyl ether 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. The substance is not included in the Authorisation list under REACH.

Classification and labelling

1,6-hexandiol diglycidyl ether is not included in Annex VI to the CLP regulation (Regulation (EC) No 1272/2008); i.e. it is not subject to harmonised classification.

Self-classification

The Classification & Labelling (C&L) inventory database at the website of the European Chemicals Agency (ECHA) contains classification and labelling information received from manufacturers and importers on substances notified and registered under REACH. 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 1,6-hexandiol diglycidyl ether listed in the database is shown in table 2. 88 (20%) of the 437 notifiers do not assign any hazard statement codes.

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

CAS No	Hazard Class and Category Code(s)	Hazard State-ment Codes	Number of notifiers
16096-31-4	Skin irrit. 2	H315	326 / 437
	Skin sens. 1	H317	326 / 437
	Eye irrit. 2	H319	326 / 437
	Aquatic Chronic 3	H412	311 / 437

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

- Skin irritation category 2: H 315 Causes skin irritation
- Skin Sensitisation category 1: H 317 May cause an allergic skin reaction
- Eye Irritation Category 2: H 319 Causes serious eye irritation
- Aquatic chronic category 3: H412 Harmful 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 1,6-HEXANDIOLDIGLYCIDYLETHER

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 1,6-hexandiol diglycidyl ether

3.2 Manufacture and use of 1,6-hexandiol diglycidyl ether in the EU

It is not known, whether the substance is produced within EU. The substance is manufactured or imported in the 1,000-10,000 t/y range. Confidential information on manufacture would be available to ECHA and Member States' authorities from registrations.

The European Council of producers and importers of paints, printing inks and artists' colours (CEPE) informs that the substance is widely used as a reactive solvent in epoxy coatings in the paint industry. It is incorporated into paint formulations in order to reduce their VOC content. The epoxy coatings in question may e.g. be used for coating for drinking water tanks [CEPE 2012].

The Association of the European Adhesive and Sealant Industry (FEICA) has assisted in obtaining information on the substance from member companies. Some adhesive companies have indicated that the substance is used as reactive dilutant in epoxy systems for buildings (two part, epoxy based adhesives, flooring and coating). The reactive dilutant contains 5-40% of the substance and the concentration of the substance in the end product will be in the range of 0-10%. No data on the consumption of the substance in the 27 EU Member States (EU27) is available [FEICA 2012].

A SDS describes the uses as follows:
"Dilutant is an organic liquid added to resin formulations, with no solvent power, to reduce viscosity and to ease flow movement or to improve the consistency and applicability. Typical applications would be for the manufacture of paints, lacquer, varnishes, adhesives, and coatings. Thinner's function is to make the application simple only and must evaporate after application. The term dilutant is also used in solvent system as an inert substance added to some other substance or solution so that the concentration volume is decreased. It is used as a general purpose dilutant to reduce viscosity of epoxy resins, favouring improved filler loading and substrate wetting and resulting in faster curing time. It is also used as a stabilizer for chlorinated vinyl resins and rubber. It is used as a chemical intermediate to make other compounds." [Chemicalland ,2012]

Other uses indicated by SDSs include material for stereolithography systems and materials useful as structural adhesives, for casting and tooling, civil engineering, composites, potting, encapsulation and crack injection.

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

The REACH registration dossiers for 1,6-hexandiol diglycidyl ether contain little information on the specific end-uses of the substance in the public part of the dossiers. The indicated end-uses include the following applications:

- Industrial coatings application

  - Market sector type: Coatings and paints, thinners, paint removers, polymer preparations and compounds
- Industrial castings applications
  - Market sector type: Intermediate, polymer preparations and compounds
- Industrial applications
  - Market sector type: Adhesives, sealants, coatings and paints, thinners, paint removers, fillers, putties, plasters, modelling clay. non-metal-surface treatment products
- DIY (do-it-yourself) consumer applications - Adhesives and Paints
  - Chemical product categories: Adhesives, sealants, coatings and paints, thinners, paint removes
  - Article categories related to subsequent service life: Vehicles ,machinery, mechanical appliances, electrical/electronic articles, stone, plaster, cement, glass and ceramic articles, metal articles, paper articles, wood articles, plastic articles
- Consumer applications
  - Chemical product categories: Adhesives, sealants, coatings and paints, thinners, paint removes, fillers, putties, plasters, modelling clay.

3.2.1 Statistics on manufacture and import/export of 1,6-hexandiol diglycidyl ether 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 1,6-hexandiol diglycidyl ether in Denmark

3.3.1 Manufacture, import, export and consumption of 1,6-hexandiol diglycidyl ether on its own

No separate commodity codes (CN8) 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 1,6-hexandiol diglycidyl ether in preparations

The Danish Coatings and Adhesives Association [DFL 2012] and the Plastic Industry in Denmark [Plastindustrien 2012] confirm the use described by CEPE as a dilutant in some epoxy systems.

Data on 1,6-hexandiol diglycidyl ether in mixtures registered in the Danish Product Register are summarised in TabLe . The data shows the total consumption i.e. content of mixtures placed on the Danish market (manufacture + import - export). Aside from the consumption of the substances in mixtures placed on the Danish market approx. 15 tons of the substance is exported in mixtures.

The Danish Product Register includes 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). As 1,6-hexandiol diglycidyl 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.

No investigations exist that can disclose the total consumption of 1,6-hexandiol diglycidyl ether in Denmark. It is deemed likely that the figures presented in table 4 underestimates the total consumption, as not all mixtures are included in the figures.

Considering that the registered tonnage band for EU is 1,000 - 10,000 t/y (see table 1) and that the population of Denmark is about 1.1% of the population in EU27, one would expect the total consumption in Denmark to be in the range of 11-110 t/y, assuming that the consumption in Denmark equals the average consumption in EU. However, considering that Denmark likely are among the more technological advanced countries in EU, the consumption in Denmark should be expected to be above the average and may potentially be about 100 t/y or even above.

TABLE 4
1,6-HEXANDIOL DIGLYCIDYL ETHER IN PREPARATIONS PLACED ON THE DANISH MARKET IN 2011 AS REGISTERED IN THE DANISH PRODUCT REGISTER

Use area	Registered consumption tonnes/year
Binders	16,69
Flooring materials	4,64
Construction materials	1,95
Adhesives	1,61
Paint and lacquers	14,73
Fillers	0,93
Other applications	2,66
Total (rounded average)	43.21

3.3.3 Import, export and consumption of 1,6-hexandiol diglycidyl ether in articles

No information on the presence of 1,6-hexandiol diglycidyl ether in articles or other end-products are available.

3.3.4 Summary on the use of 1,6-hexandiol diglycidyl ether in Denmark

The dominant use is as a reactive dilutant in epoxy systems. These epoxy systems may have many different end uses. No information on other applications is available. Based on data from the Danish Product Register, the consumption of the substance in products used professionally in Denmark can be estimated to approximately 43 tonnes/year, which represent a decrease to less than 40% of the tonnage in 2008.

However, as not all mixtures containing 1,6-hexandiol diglycidyl ether is registered in the Danish Product Register it is estimated that the total consumption in Denmark may potentially be about 100 t/y or even above.

4. Waste management

4.1 Waste from manufacture and use of 1,6-hexandiol diglycidyl ether

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

4.2 Waste products from the use of 1,6-hexandiol diglycidyl ether in mixtures and articles and recycling

No studies regarding the fate of the substance by handling of waste containing the substance in articles and mixtures are available. The fate of the substance depends strongly on how the waste is collected and treated.

Unhardened residues from application of epoxy systems should in EU be expected to be collected as chemical and hazardous waste. However, in some cases unhardened residues may also be collected as municipal waste. Recycling of the substance is not seen as relevant.

4.3 Releases of 1,6-hexandiol diglycidyl ether 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 reactive organic substance with low vapour pressure used primarily in epoxy systems, the substance would be integrated in the epoxy product, meaning that the fate of the substance is determined by the fate of the epoxy product.

For unhardened residues treated as chemical waste and disposed of by incineration the substance will most likely completely destroyed.

Hardened residues collected and treated as municipal combustible waste will generally be destroyed by the process. No certain knowledge on formation and release of substance residues or potential decomposition products from incineration processes is, however, available.

Regarding hardened residues collected and disposed of by landfilling, the environmental fate of this waste is difficult to foresee, and the epoxy material may remain intact for many years. No knowledge on formation and release of substance residues or potential decomposition products is, however, available. To the extent that 1,6-hexandiol diglycidyl ether is released from the epoxy, the substance is highly soluble in water and may thus be released from landfills through leachate. Disposal of unhardened residues by landfilling may also cause release of the substance through leachate.

The knowledge available does not allow any prediction of the fate of the substance by biological processes as composting or waste water treatment.

5. Environmental effects and fate

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

- The Danish EPA QSAR database [OASIS 2010];
- The Self-Classifications obtained from the REACH Classification& Labelling inventory (C&L inventory);
- (Material) Safety Data Sheets ((M)SDSs) (see reference list), and
- Data published on ECHA's website, database on registered substances (it has been outside the scope of this project to check original literature and IUCLID files).

5.1 Classification and Labelling

5.1.1 C&L inventory

TABLE 5
SUMMARY OF C&L INVENTORY (ENVIRONMENTAL IMPACTS)

CAS No	Hazard Class and Category Code(s)	Hazard State-ment Codes	Number of notifiers
16096-31-4	Aquatic Chronic 3	H412	311/437

5.1.2 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 1,6-hexandiol diglycidyl ether for classification as [DEPA 2009]:

- Aquatic chronic category 3: H412 Harmful to aquatic life with long lasting effects.

5.1.3 Registrations under REACH

Aquatic chronic category 3: H412 Harmful to aquatic life with long lasting effects.

5.2 Fate in the environment

5.2.1 Soil and sewage adsorption

An adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC) was found to be ca. 962 (OECD Guideline 121) [ECHA 2012].

5.2.2 Persistence

1,6-hexandiol diglycidyl ether was biodegraded approximately 47% in an OECD Testing Guideline 301D Closed Bottle biodegradation study and concluded to be inherently biodegradable under appropriate treatment conditions [ECHA 2012].

This property combined with the aquatic toxicity (see below) has triggered a classification as "Aquatic chronic category 3: H412 Harmful to aquatic life with long lasting effects" in the registration, in most C&L inventory entries (311/437) and in the identified (M)SDSs. This is also the proposed classification in the Danish Advisory list for Self-Classification, based on the Danish EPA QSAR database [DEPA 2009].

5.2.3 Bioaccumulation

Log Kow for the substance was estimated to be 0.822 in an OECD Testing guideline 107 study [ECHA 2012].

A bioconcentration factor (BCF) of 3.57 (from pH 1 - 10 at 25 C) can be estimated using the QSAR method by Advanced Chemistry Development (ACD/Labs) Software V9.04 for Solaris.

Based on this information, 1,6-hexandiol diglycidyl ether is not considered to have a bioaccumulation potential.

5.3 Environmental effects

5.3.1 Aquatic

Fish acute
96 hr LC_{50} values of 30 mg/L (semi-static) and 17.1-30.9 mg/L (static) for rainbow trout were determined in studies according to OECD Testing Guideline 203 [ECHA 2012]. One MSDS indicates a similar value (30 mg/L) for *leuciscus idus* and another MSDS indicates "Freshwater fish" LC_{50}: 10-100 mg/L. None of these MSDSs indicate the references.

Invertebrates acute
A 48 hr static EC_{50} value of 47 mg/L for *Daphnia magna* was determined in a study according to OECD Testing guideline 202 [ECHA 2012]. One MSDS indicates "Freshwater invertebrate" LC_{50}: 10-100 mg/L without indicating the reference.

Algeae
A 48 hr LC_{50} value for green algae of 23.1 mg/L was estimated using the OECD. MultiCASE QSAR model [ECHA 2012].

No long-term aquatic and no terrestrial toxicity studies have been identified.

Aquatic microorganisms
An IC50 (180 min) > 100 mg/L was estimated in an Activated Sludge, Respiration Inhibition Test according to OECD Testing Guideline 209 [ECHA 2012].

These data combined with the inherent biodegradability of the substance (see above) has triggered a classification as "Aquatic chronic category 3: H412 Harmful to aquatic life with long lasting effects" in the registration, in most C&L inventory entries (311/437) and in the identified (M)SDSs. This is in line with the Danish EPA QSAR database [OASIS 2010] suggestion.

5.4 Summary

Based on the available information, 1,6-hexandiol diglycidyl ether appears to be inherently persistent with low potential for bioaccumulation.

1,6-hexandiol diglycidyl ether has been tested for acute ecotoxicity in rainbow trout and *Dapnia* and toxicity to algae has been predicted using QSAR. EC50/LC50 values (48 and 96 hours) in the 20-50 mg/L range have been found.

Based on the above, a classification as "Aquatic chronic category 3: H412 Harmful to aquatic life with long lasting effects" is triggered in the registration, in most C&L inventory entries (311/437) and in the identified (M)SDSs. This is in line with the Danish EPA QSAR database suggestion.

1,6-hexandiol diglycidyl ether was not toxic to microorganisms in an Activated Sludge, Respiration Inhibition Test.

No long-term aquatic or terrestrial toxicity studies have been identified.

6. Human health effects

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

- The Danish EPA QSAR database [OASIS 2010]:
- The Self -Classifications obtained from the REACH Classification & Labelling inventory (C&L inventory);
- (Material) Safety Data Sheets ((M)SDSs) identified (see reference list);
- Articles (peer-reviewed) identified (only abstracts have been screened within the scope of this project), and
- Data published on ECHA's website, database on registered substances. (it has been outside the scope of this project to check original literature and IUCLID files).

6.1 Classification and Labelling

6.1.1 C&L inventory

TABLE 6
SUMMARY OF C&L INVENTORY (HUMAN HEALTH)

CAS No	Hazard Class and Category Code(s)	Hazard State-ment Codes	Number of notifiers
16096-31-4	Skin irrit. 2	H315	326/437
	Skin sens. 1	H317	326/437
	Eye irrit. 2	H319	326/437

- Skin irritation category 2: H 315 Causes skin irritation
- Skin Sensitisation category 1: H 317 May cause an allergic skin reaction
- Eye Irritation Category 2: H 319 Causes serious eye irritation

6.1.2 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 1,6-hexandiol diglycidyl ether for classification as [DEPA 2009]:

- Skin irritation category 2: H 315 Causes skin irritation (R38)
- Skin Sensitisation category 1: H 317 May cause an allergic skin reaction (R43)
- Carcinogenicity category 3: H351 Suspected of causing cancer (Carc. 3 R40)

The classification as Carc 3; R40, has triggered the listing of 1,6-hexandioldiglycidylether on the List of Undesirable Substances (LOUS), 2009.

6.1.3 Registrations

- Skin irritation category 2: H 315 Causes skin irritation (R38)
- Skin Sensitisation category 1: H 317 May cause an allergic skin reaction (R43)
- Eye Irritation Category 2: H 319 Causes serious eye irritation (R36)

6.2 Biokinetics - ADME

[Boogaard *et al*. 2000a] studied the percutaneous penetration and metabolism of 1,6-hexandiol diglycidyl ether in the fresh, full-thickness C3H mouse, and Fisher 344 rat and dermatomed human skin to determine the apparent permeability constants, lag times and metabolic profiles *in vitro*. The percutaneous absorption was highest for mouse skin (80.3%), in between for rats (67.2%) and lowest for dermatomed human skin (37.8%). Unchanged and metabolised 1,6-hexandiol diglycidyl ether (1,6-hexandiol diglycidyl ether (bis-)diol) was found following the penetration in the species studied.

[Boogaard *et al*. 2000b] studied the metabolic inactivation of 5 glycidyl ethers (GE) in subcellular fractions of lung and liver from humans, rats and mice *in vitro*. 1,6-hexandiol diglycidyl ether can be metabolically inactivated by epoxide hydrolase (EH) and gluthtahione S-transferase (GST), although less efficiently than other GEs.

6.3 Acute toxicity

Oral
1,6-hexandiol diglycidyl ether has been tested in three rat species showing LD_{50} values in the range of 2,000-4,000 mg/kg, except for female Wistar rats (1681 mg/kg) [ECHA 2012]. This possible outlier is not considered sufficient for triggering a classification by the CSR registrant. Two of the identified (M)SDS lists LD_{50} values of 2900-8500 (rat) and >8500 (rabbit) without indicating the reference. The substance has not been classified for acute oral toxicity in the C&L inventory or in any of the identified (M)SDSs.

Inhalation
There were no mortalities at the highest concentration tested (35 mg/m^3 = the maximal vapour concentration achieved) in an OECD 433 rat study [ECHA 2012].

Dermal
In a limit dose test in rats, no mortalities were observed at 2000 mg/kg [ECHA 2012]. Two of the identified (M)SDSs list LD50 values of >2000 (rat) and >4900 (rabbit) without indicating the reference.

Overall, 1,6-hexandiol diglycidyl is of low toxicity based on animal studies. In line with this the Danish EPA QSAR database does not suggest classifications for acute toxicity [Oasis 2010].

6.4 Skin and eye irritation

Three dermal rabbit studies (two of which are draize tests) indicate the substance to be irritating/highly irritating [ECHA 2012]. One eye irritation rabbit study indicate the substance to be moderately irritating [ECHA 2012].

Based on these studies, 1,6-hexandiol diglycidyl ether is proposed in the CSR to be classified as:

- Skin irritation category 2: H 315 Causes skin irritation
- Eye Irritation Category 2: H 319 Causes serious eye irritation

This is supported by 326/437 self-classifications (C&L inventory) and similar classifications R37 or R 38 in the identified (M)SDSs.

6.5 Sensitisation

A guinea pig optimization test and a mouse LLNA assay conclude that 1,6-hexandiol diglycidyl ether is a skin sensitizer [ECHA 2012]. This conclusion is confirmed by patch tests on epoxy resin workers having developed contact dermatitis [Geier *et al*., 2004; Angelini *et al*., 1996]. 1,6-hexandiol diglycidyl ether is consistently classified as skin sensitisation category 1: H 317 May cause an allergic skin reaction.

This is in line with the proposed classification in the Danish EPA QSAR database [Oasis 2010].

6.6 Repeated dose toxicity

Oral
1,6-hexandiol diglycidyl ether was tested in a combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test in rats (oral gavage, males treated for a minimum of 28 days, females for 39 days) according to OECD Guideline 422 [ECHA 2012]. A NOAEL of 200 mg/kg/day was identified based on reduced body weight, reduced food consumption and possible target organ effects (including the glandular stomach) at the highest dose level (500 mg/kg/day) [ECHA 2012].

Inhalation
1,6-hexandiol diglycidyl ether was tested in a 28 day (6h/d, 5d/w) repeated dose inhalation study (OECD 412) [ECHA 2012]. The highest dose tested showed 'minimal evidence of nasal tract inflammation'. The highest dose of 16.16 µg/L was indicated to be the NOAEL, and 4.04 µg/L as a NOEL.

6.7 Mutagenicity/carcinogenicity

The Danish EPA QSAR database [OASIS 2010] suggests the classification "Carcinogenicity category 3: H351 Suspected of causing cancer".

1,6-hexandiol diglycidyl ether is positive (with and without metabolic activation) in some *S. typhimurium* strains in the Reverse Mutation Test and negative in two *in vivo* studies (micronucleus assay and unscheduled DNA synthesis - DNA damage and/or repair). In a weight of evidence approach in the CSR, 1,6-hexandiol diglycidyl ether is considered not genotoxic. [ECHA 2012].

1,6-hexandiol diglycidyl ether is mentioned as a structural analogue to n-Butyl Glycidyl Ether (BGE) in a review of the toxicological literature [NTP 2004] showing more substantial evidence of genotoxicity for BGE.

In contrast to the classification proposed by the Danish EPA QSAR database, no C&L inventory entries nor any (M)SDS have classified the substance for this endpoint.

No studies on chronic effects or long-term carcinogenicity have been identified.

6.8 Toxicity for Reproduction

No reproductive adverse findings were identified in the Developmental Toxicity Screening Test described under repeated dose toxicity (Section 6.6).

No long-term studies for this endpoint have been identified, but the CSR suggests two testing proposals:

- Toxicity for reproduction: OECD Guideline 416 (Two-Generation Reproduction Toxicity Study)
- Developmental toxicity / teratogenicity: OECD Guideline 414 (Prenatal Developmental Toxicity Study).

6.9 Summary

Based on the identified information, 1,6-hexandiol diglycidyl ether appears to possess low acute toxicity following oral, inhalation and dermal exposure, even though an *in vitro* test suggests that the substance has the potential for significant dermal absorption.

1,6-hexandiol diglycidyl ether is a skin and eye irritant, and a skin sensitizer. The latter is confirmed by human evidence.

Similarly, 1,6-hexandiol diglycidyl ether appears to pose low repeated dose toxicity following the results of 28 days oral and inhalation studies in rats.

A developmental toxicity screening test showed no adverse reproductive effects.

The Danish Advisory list for Self-Classification, based on the Danish EPA QSAR database OASIS and structural analogues to 1,6-hexandiol diglycidyl ether indicate that the substance may poses genotoxic/carcinogenic properties. 1,6-hexandiol diglycidyl was positive in one bacteria *in vitro* genotoxicity test, but negative in two *in vivo* genotoxicity tests. No studies on chronic effects or long-term carcinogenicity have been identified. Therefore, this endpoint might require further consideration. Also, the CSR suggests further testing on reproductive toxicity end-points.

7. Monitoring data and exposure

7.1 Monitoring of 1,6-hexandiol diglycidyl ether in the environment and releases from point sources

1,6-hexandiol diglycidyl ether 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 1,6-hexandiol diglycidyl ether in the environment and releases from point sources.

TABLE 7
1,6-HEXANDIOL DIGLYCIDYL ETHER INCLUDED IN THE NATIONAL MONITORING AND ASSESSMENT PROGRAMME FOR THE AQUATIC AND TERRESTRIAL ENVIRONMENT, NOVANA 2011-2015

Substance	Point sources	Streams	etc.
16096-31-4	Not included	Not included	Not included

TABLE 8
MOST RECENT MONITORING DATA FOR 1,6-HEXANDIOL DIGLYCIDYL ETHER 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
16096-31-4			No data			

7.2 Human exposure and biomonitoring

No data are available.

7.2.1 Intake of 1,6-hexandiol diglycidyl ether

No data are available.

7.2.2 Human biomonitoring data

No data are available.

TABLE 9
BIOMONITORING DATA OF 1,6-HEXANDIOL DIGLYCIDYL ETHER

Population group	Specimen	Median concentration µg/L	Number of samples	Country	Year	Data source
		No data				

8. Information on alternatives

CEPE [CEPE 2012] and adhesives companies reporting to FEICA [FEICA 2012] have identified butanediol diglycidyl ether, C12-14 glycidyl ether, p-tert butylphenyl glycidyl ether and propanetriol triglycidyl ether as alternatives to 1,6-hexandiol diglycidyl ether.

Table 10 presents harmonised classification for these alternatives. It is noted that at least one of the alternatives presented (C12-14 glycidyl ether) seems to be less irritating and less toxic than 1,6-hexandiol diglycidyl ether. However, it is not known whether this alternative is appropriate for all applications.

TABLE 10
CLASSIFICATION OF ALTERNATIVES TO 1,6-HEXANDIOL DIGLYCIDYL ETHER)

Alternative	CAS No.	Index No	Hazard Class and Category Code(s)	Hazard statement Code(s)
Butanediol diglycidyl ether *1	2425-79-8	603-072-00-7	Acute Tox. 4 * Acute Tox. 4 * Eye Irrit. 2 Skin Irrit. 2 Skin Sens. 1	H332 H312 H319 H315 H317
C12-14 glycidyl ether *1	68609-97-2	603-103-00-4	Skin Irrit. 2 Skin Sens. 1	H315 H317
p-tert butylphenyl glycidyl ether *2	3101-60-8	No harmonised classification	Carc3; R40 (Carc. 2) Mut3;R68 (Muta. 2) R43 (Skin sens. 1) N;R50/53 (Aquatic Acute 1, Aquatic Chronic 1)	(H351) (H341) (H317) (H400) (H410)
Propanetriol triglycidyl ether *3	90529-77-4	No harmonised classification	Skin Irrit. 2 (25) Skin Sens. 1 (20) Eye Irrit. 2 (23) Acute Tox. 4 (2) Eye Irrit. 2A (1)	H315 H317 H319 H302 H319
1,6-Hexandiol diglycidyl ether (for comparison	16096-31-4	No harmonised classification	Skin irrit. 2 Skin sens. 1 Eye irrit. 2 Aquatic Chronic 3	H315 H317 H319 H412

*1 According to Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation, EC 2008)

*2 According to the Danish EPA's "Effektlisten" (DEPA, 2010); Conversion to CLP terms in brackets.

*3 The substance is preregistered under REACH. The hazard classes and codes stated are based on self-classification. A total of 25 notifications have been made. (The number of notifications for each hazard class is stated in brackets)

CEPE [CEPE 2012] informs that no alternatives are available without affecting the performance of the paint and that it will be difficult to find any alternatives to this substance for the following reasons:

- Reactive diluents are a necessity for these solvent-free products.
- This reactive diluent has better technical properties than other reactive diluents.
- Replacing one substance in the formulation requires a significant effort related to research and development, testing and product approval concerning contact with drinking water, etc.
- Replacing this reactive diluent with another reactive diluent will not reduce the sensitising potential of the products and the costs of replacement will therefore not be beneficial.

Adhesives companies reporting to FEICA [FEICA 2012] report that alternatives are not easy to find, because 1,6-hexandiol diglycidyl ether is regarded as a safer substitute for cresyl glycidyl ether in several applications where a low viscosity epoxy system with good mechanical properties is required.

The cost for the alternatives is deemed to be approximately 50 % higher. Moreover, certain alternatives will result in a worse MAL-code and it is questionable whether the toxicity level is lower.

The data presented in Table 10 indicate that alternatives to the substance exist. At least one of the alternatives presented (C12-14 glycidylether) appear to be less irritating and less toxic than 1,6-hexandiol diglycidyl ether. However, it is not known whether this alternative is appropriate for all applications.

9. Abbreviations and acronyms

BCF	BioConcentration Factor
BGE	Butyl Glycidyl Ether
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)
CSR	Chemical Safety Report
C&L	Classification and labelling
CN8	Statistical classification system (commodity statistics)
CMR	Carcinogenicity, Mutagenicity, Reproduction
DEPA	Danish Environmental Protection Agency
DNA	Deoxyribonucleic acid
EC	European Community
EC50	Median Effective Concentration (required to induce a 50% effect)
ECHA	European Chemicals Agency
EEC	European Economic Community
EH	Epoxide hydrolase
ESIS	ESIS (European chemical Substances information System)
EPA	Environmental Protection Agency
EU	European Union
EU27	European Union including 27 member states
EuPC	European Plastics Converters
FEICA	The Association of the European Adhesive and Sealant Industry
GE	Glycidyl ethers
GST	Gluththahione S-transferase
Hg	Mercury
HPLC	High Performance Liquid Chromatography
IC50	The concentration of an inhibitor where the response (or binding) is reduced by half
IUCLID	International Uniform Chemical Information Database
Koc	Soil Organic Carbon-Water Partitioning Coefficient
Kow	Octanol-Water Partition Coefficient
LC50	LC_{50} is the dose required to kill half the members of a tested population after a specified test duration.
LOUS	List Of Undesirable Substances
MSDS	Material Safety Data Sheet
NOAEL	**N**o **O**bserved **A**dverse **E**ffect **L**evel - the highest tested concentration of a chemical at which no adverse effect is found
NOEL	**N o E**ffect **l**evel - The highest tested concentration of a chemical producing no toxicological effects

NOVANA	Danish National Monitoring and Assessment Programme for the Aquatic and Terrestrial Environment
OECD	The Organisation for Economic Co-operation and Development
QSAR	Quantitative Structure–Activity Relationship
PBT	Persistent bioaccumulative toxic (chemical)
pH	A measure of acidity level (actually a measure of the activity of the solvated hydrogen ion
REACH	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
UV	Ultra Violet (light)
vPvB	very Persistent very Bioaccumulative (chemical)

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