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SUPPORT ON INPUT TO HEALTH AND ENVIRONMENTAL DISCHARGES – QUALITY CHECK OF DATA SHEETS FOR ALTERNATIVE SOLVENTS

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SINTEF REPORT

TITLE

TCM Amine Project: Support on input to health and environmental discharges

Quality check of data sheets for alternative solvents (version 2 with limited data information)

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ABSTRACT

In this report the potential Health and Environment (HE) information for solvents relevant for TCM amines are described. The data presented here should be used as a background for the TCM health and environmental risk assessment (HEIA).

Available health- and environment data relevant for REACH registration were collected from various databases, including different MSDS, the International Uniform ChemicaL Information Database (IUCLID), the Registry of Toxic Effects on Chemical Substances (RTECS), the ECOTOX database of the US Environmental Protection Agency (EPA), the BIODEG database of the Syracuse Research Centre (SRC), the RepDose Database of Fraunhofer ITEM and from scientific literature and reports. The compiled data from the different sources have been used for identifying GAPS which must be filled to meet the requirements of the Norwegian Climate and Pollution Agency (KLIF) in the TCM HEIA. The report also includes recommendations of necessary tests to fill the GAPS. In addition data acquired by (Q)SAR methods have been collected as a potential supplement to the test data, especially for solvents with limited HE-data.

A number of 12 solvents were included for HE data collection. All solvents were pre-registered in REACH with registration date 2010-11-30. The available REACH relevant data sets for the solvents differed. For some of them information relevant for all endpoints were available, although data quality could be categorized in different levels from well to poorly characterized test methods and quality assurance systems. However, some solvents lacked most of the necessary data. Partly based on available HE data the number was reduced to 8 relevant solvents. For each of these solvents the necessary test requirements were addressed to fill gaps to meet the demands required by the REACH Directive. In addition, simple (Q)SAR estimations were used to predicts potential toxicity endpoints, including those without available data.

Available health information was further investigated by for 5 solvents, including non-public RTECS information and GESAMP EHS Composite list of hazard profiles, in addition to the data sources described above.

KEYWORDS	ENGLISH	NORWEGIAN
GROUP 1	Environment/Health	Miljø/Helse
GROUP 2	Absorption	Absorpsjon
SELECTED BY AUTHOR	CO_2 capture	CO_2 håndtering
	Amines	Aminer

Abbreviations and explanations

ACC – Aker Clean Carbon ASA

BCF – BioConcentration Factor

BP – Biodegradation Propability

BW – Body Weight

CAS – Chemical Abstracts Services on collection of disclosed chemical substance information

Dermal - Substance applied to skin, usually braded. Exposure may be open or occluded (occluded is standard)

EC-50 – Effective Concentration inhibing populations of organisms by 50 %

EC - Europe

ECHA – European Chemical Agency

EINECS - European INventory of Existing Commercial chemical Substances

EPA – U.S. Environmental Protection Agency

EU – European Union

GESAMP - IMO/FAO/UNESCO/IOC/WMO/WHO/IAEA/UN/UNEP Joint Group of Experts on the Scientific Aspects of Marine Environmental Protection, 2002. Revised GESAMP Hazard Evaluation Procedure for Chemical Substances Carried by Ships

GLP – Good Laboratory Practice

HEIA – Health and Environmental Impact Assessment

HPLC – High-Pressure Liquid Chromatography

HE – Health and Environment

ICE - Isolated Chicken Eye Test Method for identifying Ocular Corrosives and Severe Irritants

Inhalation – Exposure to vapour, mist or aerosols. Experiment may use nose/mouth exposure only or the entire animal in a exposure chamber

ISO International Organization for Standardization

IUCLID – International Uniform ChemicaL Information Database

KLIF – The Norwegian Climate and Pollution Agency

LC – Lethal concentration

LC-50 – Concentration causing 50 % lethality for a population of uniform organism

LD – Lethal dose

LD-50 – Dose causing 50 % lethality for a population of uniform organism

LDL0 – Lowest lethal dose observed

LLNA – Skin sensitization: Local Lymph Node Assay

LOAEL - Lowest-Observed Adverse Effect Level

MNvit – In Vitro Mammalian Cell Micronucleus Test

MSDS – Material, Safety Data Sheet

NIOSH – US National Institute for Occupational Safety and Health

NOAEL – No-Observed Adverse Effect Level

OECD - Organisation for Economic Cooperation and Development

Oral - Substance delivered to the stomach by lavage, food or drink

PEC – Predicted Environmental Concentration

PNEC – Predicted No-Effect Concentration

Pow – Partition Coefficient between Octanol and Water

REACH - European Directive for Registration, Evaluation, Authorisation and restriction of Chemicals

Repeated Dose – Repeated dosing over time – continuous or intermitting

Reproduction, Developmental, Teratogenicity – Combines all effects on the ability to reproduce healthy offspring

RTECS – Toxic Effects on Chemical Substances®: Number indicate record number

QA – Quality Assurance

(Q)SAR – (Quantitative) Structure-Activity Relationship

SRC - Syracuse Research Centre

TC – Toxic concentration (death has occurred)

TCM - Technology Centre at Mongstad

TDL0 – Lowest dose at which toxic effects were observed

TER - In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test

TWA – Time weight average

WHO – World Health Organization

EXECUTIVE SUMMARY

In this report the potential Health and Environment (HE) information for solvents relevant for TCM amines are described. The data were based on requirements made by the Norwegian Climate and Pollution Agency (KLIF) on toxicity to health and environment, degradability, bioaccumulation, mutagenicity/genotoxicity, carcinogenic effects, reproduction toxicity, chronic toxicity, irritation/corrosion and sensitisation. The data presented here should be used as a background for the TCM health and environmental risk assessment (HEIA), and to identify gaps needed to be filled. The test requirements specified by KLIF were in accordance with recommended test methods in REACH mainly for annual production/import amounts of ≥ 10 tonnes. In addition, specific requirements are described by the European Chemical Agency (ECHA) for chronic and reproductive toxicity to reduce the number of animal tests.

Available health- and environment data relevant for REACH registration were collected from various databases, including different MSDS, the International Uniform ChemicaL Information Database (IUCLID), the ECOTOX database of the US Environmental Protection Agency (EPA), the BIODEG database of the Syracuse Research Centre (SRC), the Registry of Toxic Effects on Chemical Substances (RTECS), the Group of Experts on the Scientific Aspects of Marine Environmental Protection (GESAMP), the RepDose Database of Fraunhofer ITEM and from scientific literature and reports. Based on the compiled data from the different sources GAPS were identified which needed to be filled to meet the KLIF requirements in the TCM HEIA. The report also includes recommendations of necessary tests to fill the GAPS. In addition data acquired by (Q)SAR methods have been collected as a potential supplement to the test data.

A number of 12 solvents were included for HE data collection. All solvents were pre-registered in REACH with registration date 2010-11-30. The data sources of the available REACH relevant data sets for the solvents are shown in Table 1. The information of HE data and quality assurance (QA) system used were categorized according in 4 levels: a) Data available from standard tests with identified and available test procedures (OECD, ISO, EEC) and/or Good Laboratory Practice (GLP) QA-system, b) data available from other tests, test laboratory identified, but no GLP, c) additional data available, and d) no HE data available. For some of solvents information relevant for all endpoints were available, although data quality could be categorized in several levels as described above. However, some solvents lacked most of the necessary data.

Partly based on available HE data the number was reduced to 8 relevant solvents. For each of these solvents the necessary test requirements were addressed to fill gaps to meet the demands required by the REACH Directive, as summarised in Table 2. In addition, simple (Q)SAR estimations were used to predicts potential toxicity endpoints, including those without available data.

Available health information was further investigated by for 5 solvents, including non-public RTECS information and GESAMP EHS Composite list of hazard profiles, in addition to the data sources described above (work sub-contracted to GABYTOR). The recommendations made for these solvents were included in the summary table (Table 2).

(Q)SAR analyses indicated that some solvents had potential for genotoxicity, “high” on acute toxicity, and persistence with respect to biodegradation. (Q)SAR estimations are also of interest becacuse few HE-data were availableable for some of the solvents.

OVERORDNET SAMMENDRAG

I denne rapporten er mulige helse- og miljø- (HM) informasjon for solventer som er relevante for TCM aminer beskrevet. Datene baserer seg på krav fra Klima- og forurensningsdirektoratet (KLIF) på giftighet relatert til helse og miljø, biodegraderbarhet, bioakkumulerbarhet, mutagenitet/genotoksisitet, karsinogene effekter, reproduksjons giftighet, kronisk giftighet, irritasjon/etsing, og allergi. Dataene presentert her kan brukes som en bakgrunn for TCM helse- og miljørisiko vurdering, og for å identifisere manglende data som bør framskaffes. Testkravene spesifisert av var i samsvar med anbefalte testmetoder i REACH, hovedsakelig for årlig produksjon eller import av ≥ 10 tonn. I tillegg er spesielle krav beskrevet av det Europeiske kjemikaliebyrået (ECHA) for kronisk giftighet og reproduksjonsgiftighet for å kunne redusere antall dyretester.

Tilgjengelige helse- og miljødata som er relevante for REACH-registrering be innsamlet fra forskjellige databaser, "International Uniform ChemicaL Information Database" (IUCLID), ECOTOX databasen hos US Environmental Protection Agency (EPA), BIODEG databasen hos Syracuse Research Centre (SRC), "Registry of Toxic Effects on Chemical Substances" (RTECS), ekspertgruppen på "Scientific Aspects of Marine Environmental Protection" (GESAMP), RepDose databasen hos Fraunhofer ITEM og fra vitenskapelig litteratur og rapporter. Basert på innsamlede data fra de ulike kildene ble huller (GAP) identifisert som bør fylles for å imøtekomme KLIF sine krav til TCM en helse- og miljørisikovurdering. Rapporten inkluderer også anbefalinger for nødvendige tester som bør utføres for å imøtekomme KLIF sine krav. I tillegg er det beskrevet enkle (Q)SAR metoder som har blitt brukt for innsamling av mulige tillegg til data hentet fra reelle tester. .

Et anatll på 12 solventer ble inkludert for HM datainnsamling.Alle solventer var preregistrert i REACH med registreringsdato 30. 11.2010. Kildene for de ulike REACH-relevante datasettene er vist i Tabell 1. Informasjon om HM-data og kvalitetssikringssystemer (KS) benyttet ble kategorisert i 4 nivåer: a) Data tilgjengelige fra standardtester med identifiserte testprosedyrer (OECD, ISO, EEC) og/eller "Good Laboratory Practice" (GLP) KS-systemer, b) data tilgjengelige fra andre tester hvor testlaboratorium var identifisert, men ingen GLP, c) data tilgjengelige uten opplysninger om testprotokoller, laboratorier eller KS, og d) ingen HM-data tilgjengelige. For noen av solventene var informasjon relevant for alle endepunktene tilgjengelige, selv om dataene kunne kategoriseres i flere av nivåene nevnt over. For andre solventer manglet imidlertid de fleste nødvendige data.

Delvis basert på HM-data ble antallet relevante solventer redusert til 8. For hvert av disse ble manglende tester beskrevet som bør utføres for å imøtekomme krav fra REACH, som oppsummert i Tabell 2. I tillegg ble enkle (Q)SAR estimater brukt for å anslå potensielle endepunkter for giftighet, inkludert de det manglet testdata for.

Tilghengelig helseinformasjon ble dessuten undersøkt for 5 solventer ved bruk av RTECS informajon and GESAMP EHS liste over "hazard"-profiler, i tillegg til datakildene beskrevet over. Dette var arbeide utført av GABYTOR. Anbefalingene gjort for disse solventene ble inkludert i en oppsummeringstabell (Tabell 2).

(Q)SAR analyser indikerte at noen solventer var potensielt genotoksiske, merket som "high" for akutt toksisitet, og var persistente med tanke på biodegraderbarhet. (Q)SAR estimater var også av interesse fordi få HM-data var tiltilgjengelige for noen av solventene.

Table 1 Sources for HE-information for solvents to be evaluated for TCM.

SOLV.	IUCLID	RTECS	GESAMP	MSDS	ECOTOX	SRC	RepDose	[A)]Literature/ other
MEA	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
S1	**X**	**X**		**X**			**X**	**X**
S2	**X**			**X**				
S3	**X**	**X**	**X**	**X**		**X**		**X**
S4	**X**			**X**	**X**		**X**	**X**
S5				**X**				
S6				**X**				
S7				**X**	**X**			
S8	**X**			**X**				
S9	**X**	**X**	**X**	**X**	**X**			
S10	**X**			**X**	**X**			**X**
S11				**X**	**X**			

A) *Scientific literature related to health and effects in nature, or risk reports*

Table 2 Summary of suggested test requirements for all solvent. Parameters coloured in green require no further testing, parameters in red require more tests, while parameters in yellow should consider more testing.

Parameter	MEA	S1	S3	S4	S6	S9	S10	S11
Acute ecotoxicity								
Degradability								
Bioaccumulation								
Acute toxicity – rat								
Genotoxicity								
Irritation/corrosion								
Sensitisation								
Repeated dose Toxicity								
Reproduction toxicity								

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1 Background

The objective of the project was to collect documentation on health and environmental data for solvents and degradation products relevant for the CO_2 Technology Centre at Mongstad (TCM). This information will serve as input to the Health and Environmental Impact Assessment (HEIA) for TCM. This documentation includes a) collection and quality assurance (QA) of information on health and and environment (HE) provided by the suppliers of selected solvents relevant for TCM, b) evaluations of solvent degradation products emitted to the environment, and c) determination of environmental effects of some expected degradation products.

Specific issues described in this report include:

- Identification of alternative solvents for TCM HEIA
- Identification of sources for data – e.g. databases, scientific literature
- Collection of HE-data relevant for the HEIA – as defined by KLIF
- Comparison of data from different sources for QA
- Identifications of data GAPS
- Evaluate the use of (Q)SAR data as supplements to test data and for filling of GAPS
- Aid in the identification of necessary Health and Environments (HE)-tests to be conducted meet the requirements of the HEIA.

2 Selection of solvents

Several relevant solvents were evaluated, but Monoethanolamine (MEA) was used as a base case in this project, since MEA will be used as amine solvent during the initial phase of the TCM operation. In addition 11 coded solvents (S1 to S11) were selected. These represented both primary, secondary and tertiary amines, as well as amino acids.

3 Data requirements according to KLIF

KLIF sent the HEIA for TCM on hearing in June 2008 and received comments which were summarised in a letter to Statoil. The comments concerning HE-data for chemicals included the following requirements:

- Toxicity to health and environment
- Degradability
- Bioaccumulation
- Mutagenicity/Genotoxicity
- Carcinogenic effects
- Reproduction toxicity
- Chronic toxicity (repeated dose toxicity)
- Irritation/Corrosion
- Sensitisation

If data are inadequate for covering all these requirements the following test parameters should be used:

- Acute ecotoxicity (LC-50/EC-50) on fish, Daphnids and phytoplankton
- Biodegradability – Hydrolysis
- Bioaccumulation potential (Log Pow)
- Acute toxicity (LD-50) on rat
- Mutagenicity/Genotoxicity (*in vitro* tests)
- Irritation/Corrosion (*in vitro* tests)
- Skin sensibilisation (*in vitro* test – "LLNA")
- Repeated dose toxicity (28 days)
- Reproduction toxicity (screening test)

KLIF made some clarifications concerning results from "old tests":

- GLP is not specifically required on tests, since many tests are performed before GLP was mandatory for these kinds of tests
- New tests *must* be performed according to GLP QA system
- KLIF may further accept test results even if tests are not performed according to specified and accepted Guidelines if a) methods described can be tracked to standard accepted Guidelines, or b) there are a number of test data which are comparable

3.1.1 General test requirements according to REACH

KLIF has specified the data requirements further, as described in Table 3. These requirements are based on the REACH Directive. REACH = the new European Union EU regulation for Registration, Evaluation, Authorisation and Restriction of Chemicals (EC document "Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006).

Table 3 Requirements for HE-data and testing related to REACH . Tests recommended by KLIF are shown in light grey.

TEST PARAMETER	RECOMMENDED TEST METHODS
Ecotoxicity	***Production/import ≥ 1 tonne:*** OECD 201 - Alga, Growth Inhibition Test *and* OECD 202 - Daphnia sp. Acute Immobilisation Test ***Production/import ≥ 10 tonnes:*** OECD 203 - Fish, Acute Toxicity Test *and* OECD 209 – Activated Sludge Respiration Testing ***Production/import ≥ 100 tonnes:*** OECD 211 – Daphnia sp. Long-Term Toxicity Test *and* OECD 210 – Fish Early Stage Toxicity Test (FELS) *or* OECD 212 – Fish Toxicity Test on Embryo and Sac-Fry Stages *or* OECD 215 – Fish – Juvenile Growth Test
Degradability	***Production/import ≥ 1 tonne:*** OECD 301 - Readily Biodegradability *or* OECD 306 - Biodegradability in Seawater ***Production/import ≥ 10 tonnes:*** OECD 111 - Hydrolysis as a Function of pH (not necessary if chemical is readily biodegradable or highly soluble in water) ***Production/import ≥ 100 tonnes:*** OECD 307 – Simulation Test in Soil *or* OECD 308 – Simulation Test in Sediment *or* OECD 309 – Simulation Test in Surface Water
Fate and Behaviour in the environment	***Production/import > 1 tonne:*** OECD 107 - Partition Coefficient (n-octanol/water): Shake Flask Method *or* OECD 117 - Partition Coefficient (n-octanol/water), HPLC Method (choice of test depends on the characteristics of the chemical) ***Production/import ≥ 10 tonnes:*** OECD 106 - Adsorption/Desorption Screening ***Production/import ≥ 100 tonnes:*** OECD 305 – Bioaccumulation. Bioconcentration Flow-Through Fish Test

Table 3 Continued

TEST PARAMETER	RECOMMENDED TEST METHODS
Acute toxicity	***Production/import ≥ 1 tonne:*** OECD 420 – Acute Oral Toxicity – Fixed Dose Procedure *or* OECD 423 - Acute Oral toxicity - Acute Toxic Class Method *or* OECD 425 - Acute Oral Toxicity: Up-and-Down Procedure ***Production/import ≥ 10 tonnes:*** OECD 403 - Acute Inhalation Toxicity *or* OECD 402 - Acute Dermal Toxicity (choice of test depends on the most likely route of human exposure)
Genotoxicity / Carcinogenicity	***Production/import ≥ 1 tonne:*** OECD 471 - Bacterial Reverse Mutation Test (further tests shall be considered in the case of a positive result - see below) ***Production/import ≥ 10 tonnes:*** OECD 487 (Draft Proposal) - In Vitro Mammalian Cell Micronucleus Test (MNvit) *or* OECD 479 - Genetic Toxicology: In vitro Sister Chromatid Exchange Assay in Mammalian Cells *or* OECD 473 - In vitro Mammalian Chromosome Aberration Test OECD 476 or EC Directive 2000/32/EC B.17 - Mutagenicity - *In vitro* Mammalian Cell Gene Mutation Test (this test shall be run if negative results in tests above) ***Production/import ≥ 1000 tonnes:*** OECD 451 – Carcinogenicity Studies
Irritation/Corrosion	***Production/import ≥ 1 tonne:*** OECD 430 - In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test (TER) *or* OECD 431 - In Vitro Skin Corrosion: Human Skin Model Test *or* OECD 435 - In Vitro Membrane Barrier Test Method for Skin Corrosion OECD 437 - Bovine Corneal Opacity and Permeability (BCOP) Test method for Identifying Ocular Corrosives and Severe Irritants *or* OECD 438 - Isolated Chicken Eye (ICE) Test Method for identifying Ocular Corrosives and Severe Irritants
Skin sensitisation	***Production/import ≥ 1 tonne:*** OECD 429 - Skin Sensitisation: Local Lymph Node Assay (LLNA)

Table 3 Continued

TEST PARAMETER	RECOMMENDED TEST METHODS
Reproduction toxicity	***Production/import ≥ 10 tonnes:*** OECD 421 - Reproduction/Developmental Toxicity Screening Test *or* OECD 422 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test ***Production/import ≥ 100 tonnes:*** OECD 414 – Prenatal Development Toxicity Study *or* OECD 416 – Two-Generation Reproduction Toxicity Study
Repeated dose toxicity	***Production/import ≥ 10 tonnes:*** OECD 407 - Repeated Dose 28-day Oral Toxicity Study in Rodents *or* OECD 410 - Repeated Dose Dermal Toxicity: 21/28-day Study or OECD 412 - Subacute Inhalation Toxicity: 28-Day Study ***Production/import ≥ 100 tonnes:*** OECD 411 – Subchronic Dermal Toxicity: 90-day Study *or* OECD 413 – Subchronic Inhalation Toxicity: 90-day Study

3.2 Specific requirements for Repeated Dose Toxicity and Reproductive Toxicity

Two of the test parameters – Reproduction Toxicity and Repeated Dose Toxicity – require use of test animals, due to the lack of vitro tests. The European Chemical Agency (ECHA) has therefore described a process to reduce the number of animal tests to a minimum. Information on Reproduction and Repeated Dose Toxicities are required for production/import quantities > 100 tonnes/year.

For Repeated Dose Toxicity ECHA considers information to be complete for substances ≥ 100 tonnes/year and ≥ 1000 tonnes/year if –

1. If the substance undergoes immediate disintegration and there are sufficient data on the cleavage products, i.e. substance is readily biodegradable and degradation products are identified or predicted with relative certainty.
2. Testing does not appear scientifically necessary or is not technically possible
3. Results exist for a 90-day repeated dose toxicity study
4. Results exist for a chronic repeated dose study (≥ 12 months)
5. A testing proposal is presented for a 90-day repeated dose toxicity study
6. A testing proposal is presented for a 28-day repeated dose toxicity study

For Reproductive Toxicity ECHA considers information to be complete for substances ≥ 100 tonnes/year or ≥ 1000 tonnes/year if –

1. The substance is a known to be a) genotoxic carcinogen or a germ cell mutagen, b) to have low toxicological activity (no evidence or toxicity from available tests) or c) to have an adverse effect on fertility or developmental toxicity (data can be used for a robust risk assessment).
2. Results or testing proposal exist for a pre-natal developmental toxicity study
3. Results or testing proposal exist for a 2-generation reproductive toxicity study

4 Information tools

The tools for collection of information included –

- International Uniform ChemicaL Information **D**atabase (IUCLID)
- the ECOTOX database of the US Environmental Protection Agency (EPA)
- High Production System Information System of EPA
- Registry of Toxic Effects of Chemical Substances (RTECS)
- CHEMFATE and BIODEG databases of the Syracuse Research Centre (SRC)
- RepDose database of Repeated Dose Toxicity of Fraunhofer ITEM
- HE data sheets – including the database ECOonline
- Scientific literature and reports

Some of the databases are described closer below.

4.1 IUCLID

This information system (http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat) provides extracts of data on High Production Volume Chemicals reported by European Industry in the frame of the European existing chemicals risk assessment programme. A Chemical Data Sheet contains data on:

- General Information.
- Physico-chemical data.
- Environmental Fate and Pathways.
- Ecotoxicity.
- Toxicity related to health effects.
- References.

The system is searchable by CAS or EINECS numbers. Currently > 2500 substances are available with Chemical Data Sheets. Each substance contain a document (pdf-format) which is able to print and store locally.

4.2 RTECS

RTECS is a database of toxicity information compiled from the open scientific literature without reference to the validity or usefulness of the studies reported. Until 2001 it was maintained by US National Institute for Occupational Safety and Health (NIOSH) as a freely available publication. It is now maintained by the private company Symyx Technologies and is available only for a fee or by subscription.

Six types of toxicity data are included in the file:

- Primary irritation

- Metagenic effects
- Reproductive effects
- Turorogenic effects
- Acute toxicity
- Other multiple dose toxicity

Specific numeric toxicity values such as LD50, LC50, TDL0 and TCL0 are noted as well as species studied and the route of administration used. For all data the bibliographic source is listed. The studies are not evaluated in any way.

4.3 HPVIS

The High Production Volume Information System (HPVIS) is a database that provides access to health and environmental effects information obtained through the High Production Volume (HPV) Challenge. This program "challenges" companies to make this data publicly available on chemicals produced or imported into the United States in quantities of 1 million pounds or more per year.

On this Web site, HPVIS enables users to search for summary information, test plans, and new data on HPV chemicals as they are received by the Agency. Currently, the HPVIS database contains over 340 submissions, representing almost 900 chemical substances, either as a single chemical submission or as a member of a chemical category.

4.4 ECOTOX database

The Ecotoxicology database (ECOTOX) is a source for locating single chemical toxicity data for aquatic life, terrestrial plants and wildlife. ECOTOX was created and is maintained by the U.S.EPA (http://www.epa.gov/ecotox/). ECOTOX has integrated three previously independent databases - AQUIRE, PHYTOTOX, and TERRETOX - into a unique system which includes toxicity data derived predominately from the peer-reviewed literature, for aquatic life, terrestrial plants, and terrestrial wildlife, respectively. Only single chemical exposures are included in ECOTOX, therefore results for chemical mixtures are excluded. It should also be emphasized that bacteria and virus are not included in the ECOTOX database.

All chemicals within ECOTOX include a CAS Registry number and a chemical name and a standardized identification number and name for each chemical recorded in the database is used for consistency. Chemicals reported in the ECOTOX database are catalogued by using a Chemical Abstracts Service (CAS) registry number. If a CAS registry number is not available for the test chemical, toxicity data cannot be included in ECOTOX database.

Several test chemicals of amines are listed in the database as a function of aquatic life. The amines have been tested on different species groups, and the report does not include data of terrestrial species–only aquatic species. The tables for each amine chemical are divided into categories such as type of Species to be tested, Endpoints, BCF value, Effects measurements, Exposure duration, Exposure type, Chemical analysis, Concentration, Media type, Test location and Reference number, refers to the ECOTOX code list.

4.5 The CHEMFATE and BIODEG databases

These CHEMFATE and BIODEG databases of the Syracuse Research Corporations (SRC) are an aid in identifying persistent chemical classes, as well as physical or chemical properties that may correlate to particular behaviour in the environment (http://srcinc.com/what-we-do/efdb.aspx). These databases share a CAS# file containing over 20,000 chemicals with a preferred name and formula, and a bibliographic file containing full references on over 36,000 articles cited. They are under constant expansion, and may be accessed on the EFDB webpage (http://srcinc.com/what-we-do/efdb.aspx). Quarterly, snapshots of the databases are made available in a Microsoft Windows version and on this web site. The Windows version allows output to be printed or saved to a file, and allows searching using an ASCII file containing a list of CAS #'s.

4.6 RepDose

RepDose (repeated dose toxicity) is a relational database on subacute to chronic toxicity and currently contains 655 chemicals. The toxicity of these chemicals is documented in about 2280 studies, carried out in rats, mice or dogs with oral or inhalation exposure. The database has been developed by Fraunhofer ITEM (Bitsch et al. 2006) with funding from Cefic LRI and grows continuously.

Publicly available, predominantly peer-reviewed studies are entered in the RepDose database. Sources for data entry are a number of German, EU and WHO documents (Bitsch et al., 2006).

The qualities of the studies are ranked according to the following description: A- According to OECD guidelines or similar quality; B- Some deficiencies, but relevant for the evaluation; C- Quality cannot be assessed, (insufficient information); or D- Special design for a certain endpoint. Each chemical is characterised by at least one, but up to 15 studies, with the majority of chemicals having 1 to 4 studies. L(N)OEL values (lowest (no) observed effects level) are given for each effect and each study.

RepDose also addresses structure activity relationships (SAR), which may be utilised in integrated testing strategies to replace or reduce animal tests e.g. under REACH.

5 Available data

5.1 Data for all solvents

The available HE-related data for relevant TCM solvents are summarised and categorized in Table 4.

Table 4 HE data available for solvents relevant for TCM. The available information is categorized by colour to describe the test methods and QA-system used (GLP).

Parameter	Solvent					
	MEA	S1	S2	S3	S4	S5
Acute ecotoxicity						
Biodegradability						
Bioaccumulation						
Acute tox.-rat						
Genotox.						
Irritation/corrosion						
Sensitisation						
Repeated dose tox.						
Reproduction tox.						

Table 4 Continued.

Parameter	Solvent					
	S6	S7	S8	S9	S10	S11
Acute ecotoxicity						
Biodegradability						
Bioaccumulation						
Acute tox.-rat						
Genotox.						
Irritation/corrosion						
Sensitisation						
Repeated dose tox.						
Reproduction tox.						

Eplanation:

	Data from standard tests (OECD, ISO, EEC) and/or GLP
	Data from other tests – testing laboratory identified – no GLP
	Other available data
	No HE data available

The results of Table 4 shows that the following information related to all required parameters were available for the following solvents: MEA, S1, S3, S4, and S9. Limited HE information was available for S10 and S11, while no data at all were found for S6.

According to REACH all chemicals produced or imported in amounts > 1000 tonnes per year should be pre-registered at latest June-December 2008, with a registration deadline of December 2010, and solvents for CO_2-capture should be registered for this use. On the ECHA homepage all 12 solvents were pre-registered with the required registration deadline of December 2010.

The risk phrases have also been described for several of the solvents, according to the Classification and Labelling Database in the European Chemical Substance Information System (ESIS).

5.2 Restricting the numbers of solvents

Based on the collected information ACC decided to restrict the numbers of solvents to be evaluated for the HEIA to the following: MEA, S1, S3, S4, S6, S9, S10 and S11. These solvents were closer examined with respect to testing requirements.

Based on the requirements given by KLIF (see Table 3), and from communication with Statoil the test requirements for each of these solvents are shown in Tables 5 – 12. A summary of the test parameters requiring retesting is shown in Table 2 of the Executive Summary.

For several of these solvents the data for repeated dose and reproduction toxicity were inadequate or not available. However, ECHA has suggested to avoid unnecessary animal testing and has therefore suggested these tests may not be necessary to perform if the following information is available, as described above (see chapter 3.2). Whether these requirements are met by the available test information or not, are described in each the Tables under Comments.

Table 5 Suggested test requirements for MEA (base case solvent). Parameters coloured in green require no further testing, parameters in red require more tests, while parameters in yellow should consider more testing.

Parameter	Tests required	Tests performed	Comments (information from suppliers)
Acute ecotoxicity	**No tests**	**Phytoplankton, Daphnia, Fish GLP-tests performed for phytoplankton and invertebrates**	
Degradability	**No tests**	**Ready biodegradability (OECD 301), Marine biodegradability (OECD 306)**	
Bioaccumulation	**No tests**	**OECD 107**	
Acute toxicity	**No tests**	**Oral (rat, mouse), Dermal (rabbit)**	
Genotoxicity	**OECD 473, or OECD 479, or OECD 487 (draft)** **If negative: OECD 476**	**Several Ames tests (OECD 471):**	**One mammalian chromosome aberration test (OECD 473), and one test relevant for mammalian cell gene mutation (OECD 476) performed, both with negative test results.**
Irritation/corrosion	**No tests**	**Tests on rabbits and mice**	
Sensitisation	**No tests (?)**	**One test on guinea pigs**	**Five skin sensitisation tests performed (OECD 406) – all negative**
Repeated dose Toxicity	**No tests**	**Oral (rat) and inhalation (dog)**	**ECHA-demands met by a) MEA is readily biodegradable and suspected degradation products identified, b) a 90-days repeated dose tox test performed**
Reproduction Toxicity	**No tests (?)**	**Oral (rat)**	**Supplier information: Several tests on prenatal development (OECD 414) performed, and one test on two-generation reproduction toxicity (OECD 416) to be finished.** **All tests negative** **ECHA demands met by the fact that tests are performed for both reproduction toxicity and developmental toxicity/teratogenicity.** **Requirements for new test should be considered by KLIF or by a third part.**

Table 6 Suggested test requirements for S1. Parameters coloured in green require no further testing, parameters in red require more tests, while parameters in yellow should consider more testing.

Parameter	Tests required	Tests performed	Comments (information from suppliers)
Acute ecotoxicity	No tests	Phytoplankton, Daphnia and fish GLP-tests performed for invertebrates and fish	
Degradability	OECD 111	Biodegradability (OECD Guidelines 301, OECD 306 and EPA/FIFRA methods)	No need for further biodegradability tests, but a hydrolysis test is required due to low biodegradability. SINTEF has performed a preliminary hydrolysis test in SOLVit, showing no hydrolysis in water at 50°C for 5 days
Bioaccumulation	No tests	Octanol-water method and fish bioaccumulation tests	both tests showing low bioaccumulation potential
Acute toxicity	No tests	Oral (rat) and dermal (rabbit)	
Genotoxicity	OECD 471, and OECD 473, or OECD 479, or OECD 487 (draft) If negative: OECD 476	One Ames test	
Irritation/corrosion	No tests	Skin/eye irritation (rabbit)	
Sensitisation	No tests	Buehler test – Guinea pig (part of OECD 406)	
Repeated dose Toxicity	No tests	Oral (rat) and inhalation (rat) Other tests on monkey, dog and Guinea pig	ECHA-demands met by the fact that a 90-days repeated dose tox test has been performed.
Reproduction Toxicity	No tests (?)	OECD 421/OECD 414 (rats)	ECHA demands met by the fact that tests have been performed for developmental toxicity/teratogenicity. Requirements for new test should be considered by KLIF or by a third part.

Table 7 Suggested test requirements for S3. Parameters coloured in green require no further testing, parameters in red require more tests, while parameters in yellow should consider more testing.

Parameter	Tests required	Tests performed	Comments (information from suppliers)
Acute ecotoxicity	No tests	Phytoplankton, Daphnia and fish Tests performed by defined guidelines (DIN, EWG or ISO). One GLP-test performed for fish	
Degradability	No tests	OECD Guidelines (GLP-test)	
Bioaccumulation	No tests	Octanol-water test	
Acute toxicity	No tests	Oral (rat) and dermal (rabbit)	
Genotoxicity	No tests	Several Ames tests, HGPRT assay, mammalian cell gene mutation, sister chromatid exchange assays and Micronucleus assay	
Irritation/ Corrosion	No tests	Skin and eye tests (rabbit)	
Sensitisation	No tests	Maximimization test - part of OECD 406 (Guinea pig)	
Repeated dose Toxicity	No tests (?)	90-day test (rat), 13-week dermal test (rat)	ECHA-demands met by a) MDEA is readily biodegradable and suspected degradation products identified, b) a 90-days repeated dose tox test performed
Reproduction Toxicity	No tests (?)	Development toxicity/teratogenicity (rats) Dermal exposure(species ??), 6-15 days)	Supplier information: One test on prenatal development (OECD 414) performed, no information given on test results. ECHA demands possibly met by the fact that a test has been performed for developmental toxicity/teratogenicity. Requirements for new test should be considered by KLIF or by a third part.

Table 8 Suggested test requirements for S4. Parameters coloured in green require no further testing, parameters in red require more tests, while parameters in yellow should consider more testing.

Parameter	Tests required	Tests performed	Comments (information from suppliers)
Acute ecotoxicity	**No tests**	**Phytoplankton, Daphnia and fish: Phytoplankton and invertebrate tests performed by OECD Guidelines 201 and 202, respectively (SINTEF).**	
Degradability	**OECD 111**	**OECD 301 (ready biodegradability, OECD 302 (inherent biodegradability) and OECD 306 (marine biodegradability). Hydrolysis test performed by SINTEF**	
Bioaccumulation	**No tests**	**Fish (OECD 305 (fish)**	
Acute toxicity	**No tests**	**Oral (rat) and dermal (rabbit)**	
Genotoxicity	**No tests**	**Several Ames tests Several *in vitro* and *in vivo* tests - Mammalian cell tests – OECD 473-GLP; Mouse lymphoma assays (GLP), Micronucleus assay (GLP)**	
Irritation/ Corrosion	**No tests**	**Several skin tests on rabbits, (OECD 404) and eyes. Human *in vivo* test**	
Sensitisation	**No tests**	**Guinea pig maximization test (part of OECD 406) and human Patch test**	
Repeated dose Toxicity	**No tests**	**90-days repeated dose tox test (rat)**	**Full risk assessment performed for this solvent**
Reproduction Toxicity	**No tests**	**Reproduction toxicity Developmental toxicity/teratogenicity (OECD 414-GLP)**	**Full risk assessment performed for this solvent**

Table 9 Suggested test requirements for S6. Parameters coloured in green require no further testing, parameters in red require more tests, while parameters in yellow should consider more testing.

Parameter	Tests required	Comments	Further information from supplier
Acute ecotoxicity	OECD 201 OECD 202 OECD 203	No ecotoxicity tests performed	
Degradability	OECD 301 (OECD 111)	No tests performed. A hydrolysis test is required if not readily biodegradable	
Bioaccumulation	OECD 107, or OECD 117	No tests performed	
Acute toxicity – rat	OECD 420, or OECD 423, or OECD 425 OECD 402, or OECD 403	No acute tests performed	
Genotoxicity	OECD 471, and OECD 473, or OECD 479, or OECD 487 (draft) If negative: OECD 476	No genotoxicity tests performed	
Irritation/ Corrosion	OECD 430, or OECD 431/435 and OECD 437, or OECD 438	No tests performed	
Sensitisation	OECD 429	No tests performed	
Repeated dose Toxicity	OECD 407, or OECD 410, or OECD 412	No tests performed	
Reproduction Toxicity	OECD 421, or IECD 422	No tests performed	

Table 10 Suggested test requirements for S9. Parameters coloured in green require no further testing, parameters in red require more tests, while parameters in yellow should consider more testing.

Parameter	Tests required	Tests performed	Comments (information from suppliers)
Acute ecotoxicity	No tests	Phytoplankton, Daphnia and fish: LC50 Tests performed by OECD Guidelines 201, 202 and 203 and by GLP.	
Degradability	OECD 111	OECD 301 (ready biodegradability) and OECD 302(inherent biodegradability). Hydrolysis test performed by SINTEF	
Bioaccumulation	No tests	OECD 107	
Acute toxicity	No tests	Oral (rat) and dermal (rabbit)	
Genotoxicity	No tests	Ames tests (OECD 471-GLP) Cytogenetic tests performed according to OECD 473 and 476 (both GLP)	
Irritation/ Corrosion	No tests	Dermal (rabbit): Draize test (former part of OECD 405) Eye (rabbit)	
Sensitisation	No tests	Buehler test in Guinea pigs (part of OECD 406)	
Repeated dose Toxicity	No tests (?)	Oral 90 days (rat)	Supplier information: A repeated dose dermal toxicity test (OECD 410) has been performed No data ECHA-demands met by the fact that a 90-days repeated dose tox test has been performed. Requirements for new test should be considered by KLIF or by a third part.
Reproduction Toxicity	No tests (?)	OECD 421 (Information from Delamine – supplier not certain if this test has been performed) Reproduction – spermatogenesis (male rat)	Supplier information: A combined test on repeated dose and reproduction toxicity planned (OECD 421) ECHA demands met by the fact that a fertility test has been performed (OECD 421).

Table 11 Suggested test requirements for S10. Parameters coloured in green require no further testing, parameters in red require more tests, while parameters in yellow should consider more testing.

Parameter	Tests required	Tests performed	Comments (information from suppliers)
Acute ecotoxicity	OECD 201 (?) OECD 202 OECD 203	Marine phytoplankton (ISO/DIS 10253 - SINTEF)	
Degradability	OECD 301	Marine biodegradability (OECD 306 - SINTEF)	
Bioaccumulation	OECD 107, or OECD 117	No tests performed	
Acute toxicity	OECD 420, or OECD 423, or OECD 425 OECD 402, or OECD 403	Oral toxicity (rats)	
Genotoxicity	OECD 471, and OECD 473, or OECD 479, or OECD 487 (draft) If negative: OECD 476	One genotoxicity test performed (sister chromatid exchange assay)	
Irritation/ Corrosion	OECD 430, or OECD 431/435 and OECD 437, or OECD 438	No tests performed	
Sensitisation	OECD 429	No tests performed	
Repeated dose Toxicity	OECD 407, or OECD 410, or OECD 412	No tests performed	
Reproduction Toxicity	OECD 421, or IECD 422	No tests performed	

Table 12 Suggested test requirements for S11. Parameters coloured in green require no further testing, parameters in red require more tests, while parameters in yellow should consider more testing.

Parameter	Tests required	Tests performed	Comments (information from suppliers)
Acute ecotoxicity	OECD 201 (?) OECD 202 OECD 203	Marine phytoplankton (ISO/DIS 10253 - SINTEF)	
Degradability	OECD 301	Marine biodegradability (OECD 306 - SINTEF)	
Bioaccumulation	OECD 107, or OECD 117	No tests performed	
Acute toxicity – rat	OECD 420, or OECD 423, or OECD 425 OECD 402, or OECD 403	Oral toxicity (rats)	
Genotoxicity	OECD 471, and OECD 473, or OECD 479, or OECD 487 (draft) If negative: OECD 476	No tests performed	
Irritation/ Corrosion	OECD 430, or OECD 431/435 and OECD 437, or OECD 438	No tests performed	
Sensitisation	OECD 429	No tests performed	
Repeated dose Toxicity	OECD 407, or OECD 410, or OECD 412	No tests performed	
Reproduction Toxicity	OECD 421, or IECD 422	No tests performed	

6 Additional information – (Q)SAR calculations

Structure-activity relationship (SAR) methods may also be considered as a possible option in some instances, according to REACH. A number of simple approaches to SAR-calculations have been used for the TCM solvents, all of them easily accessible from the Internet, either as downloaded methods or by direct input of data on Internet versions. No programs requiring calculations by the user was used here, only methods requiring input of CAS number or SMILES.

For ecotoxicity calculations the EPISUITE systems represent an option. This system is developed and maintained by EPA. EPISUITE contains a number of modules for predictions of fate and effects in the environment.

- Biodegradation Probability Program (Biowinnt), which estimates the probability of rapid aerobic or anaerobic biodegradation of an organic chemical in the presence of mixed populations of environmental microorganisms. Biowinnt estimates are based upon fragment constants that were developed using multiple linear and non-linear regression analyses.

- ECOSAR, which predicts the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Standard version include SARs for aquatic green algae, daphnid and fish toxicity tests

In a recent study Biowinnt and Ecosar estimations were compared to measured biodegradation and ecotoxicity data for 41 amines, showing better agreement between ecotoxicity than biodegradation data (Haugmo et al., 2009).

For health-related data the following databases and predictive tools were used, both commissioned by the EU Joint Research Centre.

- *Danish (Q)SAR database*. The Danish Environmental Protection Agency has constructed a (Q)SAR database comprising predictions made by some 70 models for about 166,000 organic chemicals for a wide range of different endpoints. An internet version of the database enables different types of searching, including structure (substructure/exact match) searching, ID (CAS number, name) searching and parameter (endpoint) searching. This database includes data for both health and environmental data

- *Toxtree*. Toxtree has been designed with flexible capabilities for future extensions. Currently, plug-ins are available for applying the following rulebases: a) the Cramer classification scheme for TTC (Threshold of Toxicological Concern) estimation; b) an extended Cramer scheme; c) the Verhaar scheme for predicting the mode of toxic action in aquatic species; d) decision trees for estimating skin and eye irritation and corrosion potential, based on the BfR rules, e) the Benigni-Bossa rulebase for mutagenicity and carcinogenicity; f) the ToxMic rulebase for the in vivo micronucleus assay; g) structural alerts for the identification of Michael acceptors; and h) the START rulebase for persistance / biodegradation potential.

- *Repdose*. Repdose has been described previously in this report, since it is both a database and a predictive tool (see chapter 4.4). Based on input parameters like CAS no., name, or structure/SMILES, the repeated dose toxicity of chemicals with the closest structural

similarities are shown.

7 Conclusions – HE effects and test requirement

In this report the potential HE information for solvents relevant for TCM are described. This information is based on requirements by KLIF for environmental impact assessment, and data related to the following endpoints were evaluated:

- Toxicity to health and environment
- Degradability
- Bioaccumulation
- Mutagenicity/Genotoxicity
- Carcinogenic effects
- Reproduction toxicity
- Chronic toxicity (repeated dose toxicity)
- Irritation/Corrosion
- Sensitisation

A number of 12 amines were originally evaluated, all solvents pre-registered in REACH. Based on available HE information, and as suggested by ACC, the number of solvents was reduced to 8. The information gaps with relation to test requirements are summarised below for the 8 solvents and in Tables 5-12.

MEA

Ecotoxicity data for three trophic levels (phytoplankton, invertebrate herbivores and fish) were available. Low to moderate ecotoxicity was shown, based on acute toxicity (EC50 or LC50) > 10 mg/l for most of the tests. Most of the biodegradation test results indicated that the solvent is readily biodegradable (> 60 % biodegradable), and no bioaccumulation potential was measured by octanol-water method. *No further ecotoxicity testing is required.*

The health-related data indicated no risk of mutagenic or genotoxic effects, although only data from Ames tests are available. However, the supplier of MEA claims that data from several other genotoxicity tests exists, all with negative results. Reproduction toxicity data indicated that MEA is questionable reprotoxic and may cause developmental malformations, but no classification for reproductive effects have been made. The compound is organotoxic through all exposure routes and repeated dose experiments show changes with similar specificity as the acute dose. MEA is irritating/corrosive and has been R/S classified as this.

The US occupational limit of MEA is TWA 3 ppm.

Data are available for all required endpoints, but the quality of some of these data may be questionable. Tests performed according to GLP are available for ecotoxocity (phytoplankton and Daphnia) and for developmental toxicity/teratogenicity.

Based on the available information we suggest *that no additional tests need be performed, but it should be considered if it is necessary to perform additional tests for genotoxicity (mammalian cell cultures), sensitisation (OECD 429), and/or reproduction toxicity.*

Solvent S1
Ecotoxicity data for three trophical levels (phytoplankton, invertebrate herbivores and fish) were available, as well as data from ready biodegradation and bioaccumulation testing. *No further environmental testing is required.* For health-related testing data are available for all required endpoints. Based on the available information we suggest that *additional genotoxicity tests should be performed. It could also be considered to perform a test for reproduction toxicity*, although data from OECD tests exist.

Solvent S3
Ecotoxicity data for three trophic levels (phytoplankton, invertebrate herbivores and fish) were available. Tests for ready biodegradation and bioaccumulations are also available. *No further environmental testing are required*. Data are available for all required health-related endpoints, but the quality of some of these data may be questionable. Tests performed according to GLP are available for ecotoxicity (fish), biodegradability and for repeated dose toxicity. Based on the available information we suggest that no *further tests must be performed*. It should be *considered if it is necessary to perform a repeated dose inhalation study and a test for reproduction toxicity*.

Solvent S4
Ecotoxicity data for three trophic levels (phytoplankton, invertebrate herbivores and fish) were available. Biodegradation test results are available, as well as a bioaccumulation test with fish. *No acute ecotoxicity test is required, but a hydrolysis test (OECD 111) should be considered* due to the low biodegradability. Data are available for all required health-related endpoints, but the quality of some of these data may be questionable. Tests performed according to GLP are available for genotoxicity tests and for developmental toxicity/teratogenicity. *A thorough examination of S4 has been conducted and should be satisfactory for evaluation of this solvent, and no further health-related tests should be needed*.

Solvent S6
No HE data are available for this solvent. *A complete testing for ecotoxicity and health effects should therefore be performed*. Since this solvent is pre-registered in REACH some HE-data may be expected by the end of 2010.

Solvent S9
Ecotoxicity data for three trophic levels (phytoplankton, invertebrate herbivores and fish) were available. Both biodegradation and bioaccumulation tests have been performed. *No acute ecotoxicity tests are required, but a hydrolysis test (OECD 111) should be considered* due to the low biodegradability. The health-related data are available for all required endpoints, but the quality of some of these data may be questionable. Tests performed according to GLP are available for ecotoxicity (phytoplankton, Daphnia and fish), and for several genotoxicity tests. Based on the available information we suggest that a *repeated dose test may be performed*. However, the supplier claims that a repeated dose toxicity test has been performed, and performance of such a test may therefore not be necessary. *A reproduction toxicity test may also be considered*, but the supplier has informed that a combined repeated dose and reproduction toxicity study is planned.

Solvent S10
Only a few HE tests are available for this solvent, including a marine phytoplankton and a marine biodegradability test performed at SINTEF. In addition, one test for acute oral toxicity and one test for genotoxicity test have been performed. *A complete testing for ecotoxicity and health effects should therefore be performed to meet the KLIF requirements, although testing for*

biodegradability and acute oral toxicity may only be considered, due to available data. Since this solvent is pre-registered in REACH some HE-data may be expected by the end of 2010.

Solvent S11

Only a few HE tests are available for this solvent, including a marine phytoplankton and a marine biodegradability test performed at SINTEF. In addition, one test for acute oral toxicity has been performed. *A complete testing for ecotoxicity and health effects should therefore be performed to meet the KLIF requirements, although testing for biodegradability and acute oral toxicity may only be considered, due to available data.* Since this solvent is pre-registered in REACH some HE-data may be expected by the end of 2010.

8 References

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