Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals

Chemical/Category: **CAS No. 111-96-6, (bis(2-methoxyethyl)ether (Diglyme)**

Contents:

QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR
Diglyme (CAS No. 111-96-6)

1. Background

The High Production Volume (HPV) Challenge Program[1] is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States (U.S.) in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment and environmental fate.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1,400 sponsored chemicals. Data submitted to the Organisation for Economic Co-operation and Development (OECD) HPV Programme are also being evaluated. OPPT developed a screening-level hazard characterization that consists of an objective evaluation, conducted according to established EPA guidance[2,3], of the quality and completeness of the data set provided and is based primarily on hazard data provided by sponsors. The characterization does not draw conclusions regarding the completeness of all data generated with respect to a specific chemical or mixture. The OECD SIDS documents (SIDS Initial Assessment Profile; SIAP and SIDS Initial Assessment Report; SIAR) provide similar information. Under both the HPV Challenge and OECD HPV Programs, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. Evaluation of chemical category formation and data extrapolation(s) among category members is performed in accord with established U.S. EPA[1] and OECD[4] guidance.

In 2006 and 2007, EPA received data on uses of and reasonably likely exposures to chemicals on the Toxic Substances Control Act (TSCA) Inventory of existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule[5]. Information is collected every five years under IUR, promulgated under the authority of section 8(a) of TSCA. The most recent reports pertain to chemicals manufactured in (including imported into) the U.S. during calendar year 2005 in quantities of 25,000 pounds or more at a single site. Information is reported on the identity of the chemical manufactured or imported and the quantity, physical form, and number of persons reasonably likely to be exposed during manufacture of the chemical. For chemicals manufactured or imported in quantities of 300,000 pounds or more at a single site during calendar year 2005, additional information was reported on the industrial processing and uses of the chemical, the number of industrial processing sites and of employees reasonably likely to be exposed to the chemical at these sites, the consumer and commercial uses of the chemical and an indication whether the chemical is used in products intended for use by children under 14 years of age.

For these qualitative screening-level risk characterization documents, EPA has reviewed the IUR data to evaluate exposure potential. In addition, exposure information that may have become available through prior Agency actions has been considered, as appropriate. The resulting exposure information has been combined with the screening-level hazard characterizations to develop this qualitative screening-level risk characterization[6,7]. These screening-level risk characterizations are technical documents intended to support subsequent decisions and actions by OPPT. Accordingly, the document is not written with the goal of informing the general public. The purpose of the

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[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[4] OECD. Guidance Document on the Development and Use of Chemical Categories; http://www.oecd.org/document/7/0,2340,en_2649_34379_1947463_1_1_1_1,00.html.
[5] U.S. EPA – Basic IUR Information: http://www.epa.gov/opptintr/iur/pubs/guidance/basic-information.htm
[6] U.S. EPA Guidelines for Exposure Assessment; http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=15263
[7] U.S. EPA. Risk Characterization Program; http://www.epa.gov/osa/spc/2riskchr.htm.

qualitative screening level risk characterizations is two-fold: to support initial risk-based decisions to prioritize chemicals and inform risk management options and to identify data needs for individual chemicals or chemical categories.

2. Physical-Chemical Properties and Environmental Fate

This report was prepared using the best available data from a number of sources, but draws no conclusions regarding whether additional relevant data may exist. Diglyme is a liquid at room temperature. It is miscible with water, has high vapor pressure, and is not significantly volatile from water. It is highly mobile in soil, does not bioaccumulate (is rated B1), and does not hydrolyze under environmental pHs. In the atmosphere, it is expected to photodegrade within one day. Based on experimental data for diglyme and analogs, biodegradation of diglyme is expected to be slow and the substance is judged to be moderately persistent (P2).

3. Hazard Characterization

Aquatic Organism Toxicity. The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of diglyme to aquatic organisms is low.

Human Health Toxicity. The acute toxicity of diglyme to rats via the oral and inhalation routes of exposure is low. The target organs for toxicity following repeated exposure to diglyme via inhalation were testes (decreased sperm production) and bone marrow (atrophy). Other major effects were anemia (reduction in red blood cell count, hemoglobin, hematocrit and platelet count) and lymphoid tissue atrophy of the spleen and thymus (in male and female rats). Diglyme also affected pregnancy frequency and developing conceptuses (post-implantation loss, fetal growth, viability morphological development). A reproductive toxicity test was not submitted to address the reproductive toxicity endpoint, but data submitted from another, different test (dominant-lethal test in male rats) indicates diglyme has the potential to cause reproductive toxicity. Submitted *in vitro* gene mutation and *in vivo* chromosomal aberration tests indicated negative results.

The potential health hazard of diglyme is high based on repeated-dose toxicity to blood and blood-forming organs and developmental toxicity at relatively low doses in animal studies. Available data also indicate diglyme has the potential to cause reproductive toxicity.

4. Exposure Characterization

This exposure characterization was completed using available 2006 Inventory Update Rule (IUR) submissions. Data and information that are claimed Confidential Business Information (CBI) by the submitter were reviewed and considered by EPA in preparing this assessment but are not disclosed in this summary.

In addition, the following sources were reviewed to identify exposure and use information: the HPV Challenge Submissions, OECD SIDS Data, the Toxics Release Inventory (TRI), OSHA PEL documentation, various databases and public sources.

Diglyme was manufactured and/or imported in the United States in amounts ranging from 1,000,000 to 10,000,000 pounds in 2005. The HPV submission indicates that the chemical is used primarily as a specialty solvent in a wide variety of applications (as a reaction solvent for Grignard-reactions, reduction-reactions, alkylation-reactions, and organo-metallic reactions). Other applications include use in the coating industry and photolithography for the manufacture of semiconductor chips. Specific examples of uses from non-CBI information include uses in sealants and adhesives, automotive care products, and paints and coatings.

Exposure to Workers
The National Occupational Exposure Survey (NOES), which was conducted between 1981 and 1983, estimated a total of 207 workers potentially exposed to this chemical. Based on IUR reporting, the maximum total number of workers likely to be exposed to this chemical during manufacturing and industrial processing and use is between 100 and 999. There may be additional potentially exposed workers that are not included in this estimate since not all production volume has been accounted, and there is at least one use that contains a "Not Readily Obtainable" (NRO)

response among the submissions. This chemical has a vapor pressure of 2.96 torr at 25°C. OPPT has established 0.001 torr as a value above which worker exposures to vapors should be estimated for chemical assessments. Therefore, this chemical's vapor pressure could result in worker exposure to vapors if workers were near diglyme liquid. This chemical does not have an OSHA Permissible Exposure Limit.

The IUR-based ranking for worker exposure is high.

Exposure to General Population and the Environment
The chemical is not on the Toxics Release Inventory. Based on use information, EPA assumes for the purpose of this risk prioritization that there is potential for exposures to the general population and the environment. The IUR-based ranking for the general population and the environment is high due to the assumption that there will be exposure to this chemical.

Exposure to Commercial Workers and Consumers
Non-CBI IUR information indicates exposure to diglyme by commercial workers or consumers through adhesives and sealants, automotive care products, and paints and coatings. Based on its vapor pressure as cited above, there could be significant exposures to vapors if commercial workers or consumers are near products containing this chemical. The IUR-based ranking for commercial workers and consumers is high due to the assumption that diglyme is used in commercial worker/consumer products.

Exposure to Children
There is the possibility of exposure to children from products containing diglyme. The submitter(s) indicated that the product use information for children was not readily obtainable. Thus, the IUR-based ranking for children's exposure to diglyme is medium due to the assumption that it may be in products intended for use by children.

5. Risk Characterization

The statements and rationale provided below are intended solely for the purpose of this screening-level and qualitative risk characterization and will be used for prioritizing substances for future work in the U.S. HPV Challenge Program.

5.1. Risk Statement and Rationale

Potential Risk to Aquatic Organisms from Environmental Releases (LOW CONCERN): EPA assumes there is potential for exposure to aquatic organisms from environmental releases. Although diglyme is considered moderately persistent in the environment, it has a low acute aquatic toxicity hazard, which suggests a low concern for potential risk to aquatic organisms from environmental releases.

Potential Risk to the General Population from Environmental Releases (MEDIUM CONCERN): EPA assumes there is potential for exposure to the general population from environmental releases. Diglyme is considered to be moderately persistent in the environment. The high concern for hazard to human health (at relatively low doses in animal studies) combined with potential exposures suggests a medium concern for potential risk to the general population from environmental releases.

Potential Risk to Workers (HIGH CONCERN): Available IUR data indicate that workers may be exposed to diglyme. The high concern for hazard to human health (at relatively low doses in animal studies) combined with the likely exposures that occur in occupational settings suggests a high concern for potential risk to workers.

Potential Risk to Commercial Workers and Consumers from Known Uses (HIGH CONCERN): Available IUR data indicate that commercial workers and consumers may be exposed to diglyme. The high concern for hazard to human health (at relatively low doses in animal studies) combined with the possible exposures that occur in both commercial worker and consumer use settings suggests a high concern for potential risk to both groups.

Potential Risk to Children (HIGH CONCERN): Available IUR data indicate that children may be exposed to diglyme. The high concern for hazard to human health is important in the case of children's health because animal studies indicate this chemical is toxic to developing organisms at relatively low doses in animal studies. Therefore, the high hazard concerns combined with possible exposures suggest a high concern for potential risk to children.

5.2. Uncertainties

Diglyme may have minor uses that were not reported in IUR.

5.3. Data Needs

No data needs have been identified at this time.

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Diglyme (CAS No. 111-96-6)
[9th CI Name: bis(2-Methoxyethyl) Ether]

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SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program[8] is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,9]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1,400 sponsored chemicals. OPPT is using a hazard-based screening process to prioritize review of the submissions. The hazard-based screening process consists of two tiers described below briefly and in more detail on the Hazard Characterization website[10].

Tier 1 is a computerized sorting process whereby key elements of a submitted data set are compared to established criteria to "bin" chemicals/categories for OPPT review. This is an automated process performed on the data as submitted by the sponsor. It does not include evaluation of the quality or completeness of the data.

In Tier 2, a screening-level hazard characterization is developed by EPA that consists of an objective evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. The evaluation is performed according to established EPA guidance[2,11] and is based primarily on hazard data provided by sponsors. EPA may also include additional or updated hazard information of which EPA, sponsors or other parties have become aware. The hazard characterization may also identify data gaps that will become the basis for a subsequent data needs assessment where deemed necessary. Under the HPV Challenge Program, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. This approach often significantly reduces the need for conducting tests for all endpoints for all category members. As part of Tier 2, evaluation of chemical category rationale and composition and data extrapolation(s) among category members is performed in accord with established EPA[2] and OECD[12] guidance.

The screening-level hazard characterizations that emerge from Tier 2 are important contributors to OPPT's existing chemicals review process. These hazard characterizations are technical documents intended to support subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public. The public, including sponsors, may offer comments on the hazard characterization documents.

The screening-level hazard characterizations, as the name indicates, do not evaluate the potential risks of a chemical or a chemical category, but will serve as a starting point for such reviews. In 2007, EPA received data on uses of and exposures to high-volume TSCA existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule. For the chemicals in the HPV Challenge Program, EPA will review the IUR data to evaluate exposure potential. The resulting exposure information will then be combined with the screening-level hazard characterizations to develop screening-level risk characterizations[4,13]. The screening-level risk characterizations will inform EPA on the need for further work on individual chemicals or categories. Efforts are currently underway to consider how best to utilize these screening-level risk characterizations as part of a risk-based decision-making process on HPV chemicals which applies the results of the successful U.S. High Production Volume Challenge Program and the IUR to support judgments concerning the need, if any, for further action.

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[8] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[9] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[10] U.S. EPA. HPV Chemicals Hazard Characterization website (http://www.epa.gov/hpvis/abouthc.html).
[11] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[12] OECD. Guidance on the Development and Use of Chemical Categories; http://www.oecd.org/dataoecd/60/47/1947509.pdf.
[13] U.S. EPA. Risk Characterization Program; http://www.epa.gov/osa/spc/2riskchr.htm.

SCREENING-LEVEL HAZARD CHARACTERIZATION
Diglyme (CAS No. 111-96-6)

Introduction

The sponsor, Ferro Corporation, submitted a Test Plan and Robust Summaries to EPA for diglyme (CAS No. 111-96-6; 9th CI name: bis(2-methoxyethyl) ether) dated 31 December 2003. EPA posted the submission on the ChemRTK HPV Challenge Website on March 4, 2004 (http://www.epa.gov/chemrtk/pubs/summaries/diglyme/c15023tc.htm). EPA comments were posted on 16 May 2005. Public comments were also received and posted to the website. The sponsor did not submit updated/revised documents.

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. Summary tables of SIDS endpoints are provided herein and the structure of the chemical is provided in the appendix. The screening-level hazard characterization for environmental and human health toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Summary-Conclusion

Diglyme is a liquid at room temperature. It is miscible with water, has high vapor pressure, and is not significantly volatile from water. It is highly mobile in soil, does not bioaccumulate (is rated B1), and does not hydrolyze under environmental pHs. In the atmosphere, it is expected to photodegrade within one day. Based on experimental data for diglyme and analogs, biodegradation of diglyme is expected to be slow and the substance is judged to be moderately persistent (P2).

The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of diglyme to aquatic organisms is low.

The acute toxicity of diglyme to rats via oral and inhalation routes is low. The target organs for toxicity following repeated exposure to diglyme via inhalation were testes (decreased sperm production) and bone marrow (hypoplasia). Other major effects were anemia (reduction in red blood cell count, hemoglobin, hematocrit and platelet count) and lymphoid tissue atrophy of the spleen and thymus (in male and female rats). A reproductive toxicity test was not submitted to address the reproductive toxicity endpoint, but data submitted from a dominant-lethal test indicates diglyme has the potential to cause reproductive toxicity in male rats. Diglyme affected pregnancy frequency and developing conceptuses (post-implantation loss, fetal growth, viability morphological development). Diglyme did not induce gene mutation in vitro or chromosomal aberrations in vivo.

The potential health hazard of diglyme is high based on repeated-dose (blood and blood-forming organs) and developmental toxicity. Available data (dominant-lethal test) indicate that diglyme has the potential to cause reproductive toxicity.

No data gaps were identified under the HPV Challenge Program.

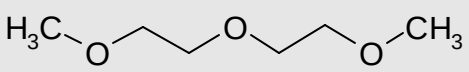
1. Physical-Chemical Properties and Environmental Fate

This report was prepared using the best available data from a number of sources, including information from the HPV test plan and robust summaries (Ferro, 2003), the Hazardous Substance Data Bank (HSDB, 2007) and estimations using EPI Suite™ (U.S. EPA, 2007).

Basic physical-chemical and environmental fate properties of diglyme are listed in Tables 1a and 1b, respectively.

Physical-Chemical Properties Characterization
Diglyme is highly soluble in water and has a high vapor pressure.

Table 1a. Physical-Chemical Properties of Diglyme

Structure		
Property	Value/Descriptor	Reference
CAS Registry No.	111-96-6	
IUPAC name	1-methoxy-2-(2-methoxyethoxy)ethane	
Molecular weight	134.17	HSDB (2007)
Physical state	Colorless liquid	HSDB (2007)
Melting point	-68° C **(m)**	Ferro Corporation (2003)
Boiling point	162° C at 760 mm Hg **(m)**	Ferro Corporation (2003)
Vapor pressure	2.96 mm Hg at 25°C **(m)** 3.49 hPa at 25°C	HSDB (2007) Ferro Corporation (2003)
Water solubility	Miscible >1000 g/L at 25°C **(m)**	HSDB (2007) Ferro Corporation (2003)
Density	0.9451 g/cm^3 at 20°C	Ferro Corporation (2003)
Log K_{ow}	-0.36 at 25° C **(m)**	Ferro Corporation (2003)

(m) denotes measured property.

Environmental Fate Characterization
Diglyme is not significantly volatile from water or moist soil surfaces. However, based on the high vapor pressure, the potential for volatilization from dry soil exists. In the atmosphere, diglyme will exist solely in the vapor phase, where it will be rapidly degraded by reaction with photochemically produced hydroxyl radicals. Diglyme is expected to be highly mobile in soil. It is not expected to undergo hydrolysis or direct photolysis in the environment due to a lack of functional groups that are susceptible to these processes. In water, diglyme is not expected to adsorb to sediment or particulate matter. Biodegradation may be a removal mechanism for diglyme in aerobic soil and water based on data on compounds with similar structures, but data from OECD ready and inherent biodegradation tests suggest that it will be relatively slow. Diglyme in soil has the potential to reach ground water resources due to its high mobility and relatively slow expected rate of degradation. Persistence and bioaccumulation are qualitatively characterized according to the criteria set forth in the PMN program (FR, 1999). As summarized in Table 2, available data are consistent with moderate persistence (i.e. rating of P2). Diglyme is not significantly bioaccumulative (i.e. it is rated B1).

Table 1b. Environmental Fate Properties of Diglyme		
Property	Value/Descriptor	Reference
Photodegradation	Half-life = 7.33 hours (calculated) Half-life = 1 day (calculated)	Ferro Corporation (2003) HSDB (2007)
Aerobic degradation	Not Readily Biodegradable The submitted data[a] were considered inadequate by EPA (U.S. EPA, 2005); however another study[b] was identified by EPA and was used to assess this endpoint	Ferro Corporation (2003)
Hydrolysis	Half-life = >1 year (calculated)	Ferro Corporation (2003)
Bioaccumulation	Not significant Estimated log BCF = 0.5 (calculated; EPI Suite 3.20)	HSDB (2007) U.S. EPA (2007)
Henry's Law Constant	$5.2x10^{-7}$ atm-m^3/mole (calculated)	HSDB (2007)
Direct photolysis	Not significant	HSDB (2007)
K_{oc}	15 mL/g (estimated)	HSDB (2007)
Fugacity	Air: 0.505% Water: 60.4% Soil: 38.9% Sediment: 0.113%	Ferro Corporation (2003)
Bioaccumulation rating	B1 (low)	
Persistence rating	P2 (moderate)	

[a] No biodegradation observed in a closed-bottle test over a 5-day incubation period and 31-42% biodegradation observed after 28 days in OECD Test Guideline 302B.
[b] 0-2% biodegradation after 28 days in OECD Test Guideline 310C; not readily biodegradable (http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html).

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

Golden orfe (*Leuciscus idus*) were exposed to diglyme at nominal concentration of 2000 mg/L under static conditions for 96 hours. No mortality was observed and no visible changes were evident at necropsy.
96-h LC_{50} > 2000 mg/L

Acute Toxicity to Aquatic Invertebrate

Daphnia magna were exposed to diglyme at nominal concentrations of 100 or 1000 mg/L under static conditions for 48 hours. There were no adverse effects observed at either concentration.
48-h EC_{50} > 1000 mg/L

Toxicity to Aquatic Plants

Green algae (*Scenedesmus subcapitatus*) were exposed to diglyme at nominal concentration of 1000 mg/L for 72 hours. No other details were provided in the robust summary.
72-h EC_{50} (growth) > 1000 mg/L

Conclusion: The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of diglyme to aquatic organisms is low.

3. Human Health Effects

Acute Oral Toxicity

(1) Male CD-1 rats were administered diglyme in water via gavageat 1500 – 23,000 mg/kg-bw and observed for 14 days. Clinical signs were restlessness unrest, disturbed sense of balance, prone position and reduced respiration rate. At high doses, there was red discharge of a red secretion from the eyes. An Approximate Lethal Dose (ALD) of for diglyme was calculated as 7500 mg/kg-bw.
LD_{50} = 7500 mg/kg-bw

Acute Inhalation Toxicity

Wistar rats (male and female) were exposed (nose only) to a saturated vapor of diglyme at greater than 11,000 mg/m^3 (11 – 14 mg/L) for 7 hours and observed 14 days after which they were sacrificed and subjected to a gross necropsy. Clinical signs were restlessness, narrowing of palpebral fissures, and irregular breathing. No mortality was seen.
LC_{50} > 11 – 14 mg/L

Repeated-Dose Toxicity

(1) Groups of 20 male and 10 female rats (Crl:CD1BR) were exposed (nose only) to diglyme vapor at 0 (control), 110, 370 or 1100 ppm (approximately 0.6, 2.0 or 6.0 mg/L/day), 6 hours/day, 5 days/week for 2 weeks. Five rats/sex/group were sacrificed after the tenth exposure and after a 2-week recovery period. The remaining five male rats/group each were sacrificed after 6- and 12-week recovery periods. Overall, male rats were more sensitive than females. In males, the primary target organs were thymus and reproductive organs (testes, epididymes, seminal vesicles and prostate). Stage specific germ cell damage occurred at all concentrations and the effects were both concentration- and time-dependent. Other treatment-related effects noted in males at every test concentration were decreased leukocyte counts at the end of the exposure period and statistically significantly ($p < 0.05$) lower mean body weights throughout the treatment period. At 1100 ppm, there was anemia (decreased red blood cell count, hemoglobin, hematocrit, and platelet count) and hematopoietic tissue atrophy (minimal to severe bone marrow hypoplasia and lymphoid tissue, atrophy of the spleen and thymus (in male and female rats) and reduced absolute and relative weights of male reproductive organs (concentration response is unclear because data and statistical analyses are not provided for relative organ weights). Evidence of hematopoietic effects in males was not seen after 42 days of recovery. The LOAEL in males was 110 ppm based on testicular atrophy, germ cell damage, reduced leukocyte count, and lower mean body weight. Data evaluation suggested a LOAEL for females of 1100 ppm based on anemia (decreased red blood cell count, hemoglobin, hematocrit, and platelet count), reduced leukocyte count, increased relative liver weight, and atrophy of hematopoietic tissues (minimal to severe bone marrow hypoplasia and lymphoid tissue atrophy of the spleen and thymus); the NOAEL was 370 ppm. NOAELs/LOAELs in this study were as follows:
LOAEL (male) ~ 0.60 mg/L/day (based on testicular effects**)**
NOAEL (male) = Not established
LOAEL (female) ~ 6.0 mg/L/day (based on hemolytic effects**)**
NOAEL (female) ~ 2 mg/L/day

The data summarized were from the only repeated-dose toxicity study provided by the sponsor. EPA considered the 14-day study adequate to address the endpoint for the purposes of the HPV Challenge Program because the effects on male reproductive organs were seen at the lowest concentration tested. The study was conducted according to GLP and the summary provided thorough details. A 28-day study (the minimum requirement to address the endpoint) would be expected to show similar, possibly exacerbated, effects. A 90-day study would strengthen the assessment by establishing NOAELs/LOAELs to properly assess systemic toxicity and characterize the hazards of diglyme.

(2) A very short description was presented in the test plan of a rat inhalation study using 0, 3.1, 9.9, 30, or 98 ppm concentrations (10 exposures followed by a 14-day recovery period), that confirms the study described above, although no robust summary for this study was provided. This study established a NOAEL of 30 ppm and a

LOAEL of 98 ppm (approximately 0.5 mg/L/day) for male rat reproductive effects, which is consistent with the study described above.

Reproductive Toxicity

A reproductive toxicity test was not submitted to address the reproductive toxicity endpoint. Data submitted for the following test indicates diglyme has the potential to cause reproductive toxicity via male germ cell mutations.

In a dominant-lethal test, adult male Sprague-Dawley rats (10/dose) were exposed via inhalation to diglyme at 0, 250 or 1000 ppm (approximately 1.4 or 5.5 mg/L/day) for 7 hours/day for 5 days. After the exposure period, the rats were serially mated with untreated virgin females, two females per male. The females were sacrificed 17 days after first being caged with exposed males and examined for evidence of pregnancy. Exposure of male rats to 1000 ppm diglyme was associated with a significant reduction in the pregnancy rate where only 50% of mated females showed evidence of implantations. The pregnancy rate was further reduced in weeks 5, 6 and 7 of mating to about 10% in females that were mated with males exposed to 1000 ppm diglyme. Diglyme also affected male fertility and embryonic development.

Developmental Toxicity

Pregnant CD-1 mice were administered diglyme via gavage at 0 (water), 62.5, 125, 250 or 500 mg/kg-bw/day daily during gestation days 6-15 and were sacrificed on day 17. Uterine contents were evaluated for the number of implantations, resorptions, late fetal deaths and live fetuses. Skeletal and external morphological abnormalities and visceral examinations of fetuses were conducted. Maternal body, uterus and liver weights were significantly decreased at the two high doses. Doses of 125 mg/kg-bw/day and above produced adverse effects on fetal growth, percent implantations, post implantation losses, fetal viability and fetal morphological development. At the highest dose, 94% of the fetuses were malformed compared to 0.35% of the fetuses in the control group.
LOAEL (maternal toxicity) = 250 mg/kg-bw/day (based on decreases in body, uterus and liver weights)
NOAEL (maternal toxicity) = 125 mg/kg-bw/day
LOAEL (developmental toxicity) = 125 mg/kg-bw/day (based on adverse effects on fetal growth, fetal viability and morphological development and malformations)
NOAEL (developmental toxicity) = 62.5 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 were exposed to diglyme at concentrations of 0, 100, 333, 1000, 3333 and 10,000 µg/plate in the presence and absence of metabolic activation. No cytotoxicity was observed at any concentration. Positive controls were tested concurrently but their responses were not provided. Diglyme was non-mutagenic in the presence and absence of metabolic activation in all four strains.
Diglyme was not mutagenic in this assay.

Genetic Toxicity –Chromosomal Aberrations

In vivo
Sprague-Dawley rats (10/sex/dose) were exposed to diglyme vapor at 0, 250 or 1000 ppm for 7 hours/day for 1 or 5 days. Animals exposed for one day only were sampled at 6, 24 and 48 hours after exposure and animals exposed for 5 days were sampled 6 hours after exposure. After the last exposure animals were injected with colchicine 2 hours prior to sacrifice, at which time bone marrow was removed, fixed and stained for examination of metaphase (50 metaphases per rat were scored). Positive controls responded appropriately. The only significant increase in abberations occurred in one low-dose male exposed for 1 day. A slight increase in total aberrations was also observed in males exposed to 250 ppm. The increase in aberrations was observed only in males and was not dose-related. The robust summary includes very brief summaries of other studies that support the non-clastogenic findings of this study.
Diglyme did not induce chromosomal aberrations in this assay.

Conclusion: The acute toxicity of diglyme to rats via oral and inhalation routes is low. The target organs for toxicity following repeated exposure to diglyme via inhalation were testes (decreased sperm production) and bone marrow (hypoplasia). Other major effects were anemia (reduction in red blood cell count, hemoglobin, hematocrit and platelet count) and lymphoid tissue atrophy of the spleen and thymus (in male and female rats). A reproductive toxicity test was not submitted to address the reproductive toxicity endpoint, but data submitted from a dominant-lethal test indicates diglyme has the potential to cause reproductive toxicity in male rats. Diglyme affected pregnancy frequency and developing conceptuses (post-implantation loss, fetal growth, viability morphological development). Diglyme did not induce gene mutation in vitro or chromosomal aberrations in vivo.

The potential health hazard of diglyme is high based on repeated-dose (blood and blood-forming organs) and developmental toxicity. Available data (dominant-lethal test) indicate that diglyme has the potential to cause reproductive toxicity.

4. Hazard Characterization

Diglyme is a liquid at room temperature. It is miscible with water, has high vapor pressure, and is not significantly volatile from water. It is highly mobile in soil, does not bioaccumulate (is rated B1), and does not hydrolyze under environmental pHs. In the atmosphere, it is expected to photodegrade within one day. Based on experimental data for diglyme and analogs, biodegradation of diglyme is expected to be slow and the substance is judged to be moderately persistent (P2).

The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of diglyme to aquatic organisms is low.

The acute toxicity of diglyme to rats via oral and inhalation routes is low. The target organs for toxicity following repeated exposure to diglyme via inhalation were testes (decreased sperm production) and bone marrow (hypoplasia). Other major effects were anemia (reduction in red blood cell count, hemoglobin, hematocrit and platelet count) and lymphoid tissue atrophy of the spleen and thymus (in male and female rats). A reproductive toxicity test was not submitted to address the reproductive toxicity endpoint, but data submitted from a dominant-lethal test indicates diglyme has the potential to cause reproductive toxicity in male rats. Diglyme affected pregnancy frequency and developing conceptuses (post-implantation loss, fetal growth, viability morphological development). Diglyme did not induce gene mutation in vitro or chromosomal aberrations in vivo.

The potential health hazard of diglyme is high based on repeated-dose (blood and blood-forming organs) and developmental toxicity. Available data (dominant-lethal test) indicate that diglyme has the potential to cause reproductive toxicity.

5. Data Gaps

No data gaps were identified under the HPV Challenge Program.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL** **Diglyme** **(111-96-6)**
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish **96-h LC_{50} (mg/L)**	> 2000
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	> 1000
Aquatic Plants **72-h EC_{50} (mg/L)** **(growth)**	> 1000
Summary of Human Health Data	
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	7500
Acute Inhalation Toxicity **LC_{50} (mg/L/6h/day)**	> 11 – 14
Repeated-Dose Toxicity **NOAEL/LOAEL (mg/L/day)** **Inhalation**	LOAEL (male) ~ 0.60 (14-d) LOAEL (female) ~ 6.0 (14-d))
Reproductive Toxicity **NOAEL/LOAEL (mg/kg-bw/day)**	A reproductive toxicity test was not submitted to address the reproductive toxicity endpoint. Data submitted from a dominant-lethal test indicate diglyme has the potential to cause reproductive toxicity via male germ cell mutations.
Developmental Toxicity **NOAEL/LOAEL (mg/kg-bw/day)** **Maternal Toxicity** **Developmental Toxicity**	 LOAEL = 250 NOAEL = 125 LOAEL = 125 NOAEL = 62.5
Genetic Toxicity – Gene Mutation ***In vitro***	Negative
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Negative

REFERENCES

Ferro Corporation. 2003. Diglyme. Robust Summaries & Test Plans. Submitted to U.S. EPA HPV Challenge Program. http://www.epa.gov/chemrtk/pubs/summaries/diglyme/c15023tc.htm

FR 1999, Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) Page 60194-60204

HSDB. 2007. Hazard Substances Data Base. As cited in HSDB record for Diglyme. Accessed August 28, 2007. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

OECD. 2006. Revised Introduction to the Organization for Economic Cooperation and Development (OECD) Guidelines for Testing of Chemicals, Section 3 (adopted 23 March 2006), paragraph 36. Available from Source OECD at http://masetto.sourceoecd.org.

USEPA. 2005. COMMENTS ON ROBUST SUMMARIES & TEST PLANS: DIGLYME
http://www.epa.gov/chemrtk/pubs/summaries/diglyme/c15023tc.htm

US EPA. 2000. Interim Guidance for Using Ready and Inherent Biodegradability Tests to Derive Input Data for Multimedia Models and Wastewater Treatment Plants (WWT) Models (9/1/2000). Part 2, Using Ready and Inherent Biodegradability Data to Derive Input Data for the EQC Model, Table 1.
http://www.epa.gov/oppt/exposure/pubs/halflife.htm#eqc.

USEPA. 2007. EPI Suite™ (version 3.2) PC-Computer software developed by the EPA Office of Pollution Prevention Toxics and Syracuse Research Corporation. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.

Screening Level Exposure Characterization for HPV Challenge Chemical

Bis (2-Methoxyethyl) ether
(Diglyme)

CAS #111-96-6

March 14, 2008

Prepared by

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Screening Level Exposure Characterization for HPV Challenge Chemical

Bis (2-Methoxyethyl) ether
(Diglyme)

CAS #111-96-6

Non-CBI Executive Summary

Diglyme [bis (2-methoxyethyl) ether] is used as a reaction solvent for Grignard-reactions, reduction-reactions, alkylation-reactions, and organo-metallic reactions in general. Other applications include in the coating industry and in photolithography for manufacture of semiconductor chips (Ferro, 2003).

Diglyme was manufactured and/or imported in the United States in calendar year 2005 (USEPA, 2006). This chemical has an aggregated volume produced and/or imported in the range of one million to ten million pounds. Persons submitting Inventory Update Reporting (IUR) information in 2006 asserted that some of the information was confidential business information (CBI) and therefore cannot be disclosed. Data and information that are CBI have been excluded from this summary.

Exposure was characterized using both public, non-confidential sources and one or more IUR submissions available at the time the exposure characterization was written. If additional information warrants an update of the exposure characterization, the update will be posted on the EPA website.

The chemical is not on the Toxics Release Inventory (USEPA, 2007a). A SIDS dossier has not been prepared for this chemical.

Exposure to Workers

This chemical has a vapor pressure of 2.96 torr at 25°C (USEPA, 2007b). OPPT has established 0.001 torr as a value above which worker exposures to vapors should be estimated for chemical assessments. Therefore, this chemical's vapor pressure could result in worker exposure to vapors if workers were proximal to the liquid. This chemical does not have an OSHA Permissible Exposure Limit (NIOSH, 2007). The National Occupational Exposure Survey (NOES), which was conducted between 1981 and 1983, estimated a total of 207 workers potentially exposed to this chemical (NIOSH, 2007b). Based on IUR reporting, the maximum total number of workers likely to be exposed to this chemical during manufacturing and industrial processing and use is between 100 and 999. There may be additional potentially exposed workers that are not included in this estimate since not all production volume has been accounted, and there is at least one use

that contains a "Not Readily Obtainable" (NRO) response among the submissions. The IUR based ranking for worker exposure is high.

Differences between numbers of workers estimated by IUR submitters and by the NOES are attributable to many factors, including time, scope, and method of the estimates. For example, NOES estimates are for all workplaces while IUR are for industrial workplaces only, and NOES used a survey and extrapolation method while IUR submitters simply provide their best estimates based on available information for the specific reporting year.

Exposure to General Population and the Environment

The chemical is not on the Toxics Release Inventory (USEPA, 2007a). Based on the totality of the information considered and expert judgment, it is assumed that potential environmental releases and subsequent exposures to the general population and the environment are likely. EPA assumes, for the purpose of this risk based prioritization, that the potential for exposures to the general population and the environment is high.

Diglyme is stable in water and not readily biodegradable; therefore diglyme is moderately persistent (P2). Diglyme is (B1) for bioaccumulation because its estimated BCF is 0.3 (USEPA, 2007b).

Exposure to Commercial Workers and Consumers

This chemical has a vapor pressure of 2.96 torr at 25°C (USEPA, 2007b). OPPT has established 0.001 torr as a value above which worker exposures to vapors should be estimated for chemical assessments. Therefore, this chemical's vapor pressure could result in worker exposure to vapors if workers were proximal to the liquid. Non-CBI IUR information indicates exposure to diglyme by commercial workers or consumers through adhesives and sealants, automotive care products, and paints and coatings. The IUR ranking for commercial workers and consumers is high due to the likelihood that there will be exposure to this chemical.

Exposure to Children

There is the possibility of exposure to children from products containing diglyme. The submitter(s) indicated that the product use information for children was not readily obtainable. The IUR ranking for children exposure is moderate that this chemical is used in products intended to be used by children, but there is uncertainty in the IUR data.

References

Ferro, 2003. Diglyme U.S. EPA HPV Challenge Program Submission. Ferro Corporation. 29 December 2003. http://www.epa.gov/chemrtk/pubs/summaries/diglyme/c15023tp.pdf

HSDB, 2007. Hazardous Substances Data Bank. Accessed December 2007, DIETHYLENE GLYCOL DIMETHYL ETHER http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?.temp/~9aU4jq:1

NIOSH, 2007. OSHA PEL Project Documentation. Accessed August, 2007. http://www.cdc.gov/niosh/pel88/npelcas.html

NIOSH, 2007b. National Occupational Exposure Survey (NOES). Accessed December 2007. http://www.cdc.gov/noes/noes2/83728occ.html

USEPA, 2006. 2006 Partial Updating of TSCA Chemical Inventory.

USEPA, 2007a. Toxic Release Inventory. Accessed August, 2007. http://www.epa.gov/tri/

USEPA 2007b. Physical/Chemical and Environmental Fate Characterization for High Production Volume Chemicals Chemical Name: Diglyme