SCREENING LEVEL HAZARD CHARACTERIZATION FOR HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Propylene Carbonate (CAS No. 108-32-7)
[9th CI name: 1,3-Dioxolan-2-one, 4-methyl-]

SUPPORTING CHEMICAL

n-Butylene Carbonate (CAS No. 4437-85-8)
[9th CI name: 1,3-Dioxolan-2-one, 4-ethyl-]

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INTERIM

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SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

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 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.

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[3].

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[2,4] 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[5] 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[4,6]. 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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[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. HPV Chemicals Hazard Characterization website (http://www.epa.gov/hpvis/abouthc.html).
[4] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[5] OECD. Guidance on the Development and Use of Chemical Categories; http://www.oecd.org/dataoecd/60/47/1947509.pdf.
[6] U.S. EPA. Risk Characterization Program; http://www.epa.gov/osa/spc/2riskchr.htm.

SCREENING LEVEL HAZARD CHARACTERIZATION
Propylene Carbonate (CAS No. 108-32-7)

Introduction

The sponsor, the Propylene Carbonate/t-Butyl Alcohol HPV Committee, submitted an initial Test Plan and Robust Summaries to EPA for propylene carbonate (CAS No. 108-32-7; 9th CI name: 1,3-Dioxolan-2-one, 4 methyl-) on April 10, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on May 2, 2002 (http://www.epa.gov/oppt/chemrtk/pubs/summaries/prplcarb/c13688tc.htm). EPA comments on the original submission were posted to the website on August 28, 2002. Public comments were also received and posted to the website. The sponsor submitted revised/updated documents on December 17, 2004, which were posted to the ChemRTK website on February 9, 2005.

This screening level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor under the High Production Volume Chemicals Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission. A summary table of SIDS endpoint data with the structure of the sponsored chemical is included 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.

Justification for Supporting Chemical

The sponsor provided data for n-butylene carbonate (CAS No. 4437-85-8) to address endpoints for acute toxicity to fish and aquatic invertebrates. Since propylene carbonate and butylene carbonate have very similar chemical structures, differing only in one alkyl group, and show similar physical-chemical properties, EPA agrees that butylene carbonate is an appropriate supporting chemical for propylene carbonate.

Summary-Conclusion

The Log K_{ow} of propylene carbonate indicates that its potential to bioaccumulate is expected to be low. Propylene carbonate is readily biodegradable, indicating that it is not expected to persist in the environment.

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

Acute toxicity of propylene carbonate via oral and dermal routes is low to rats and rabbits respectively. Repeated exposure via oral and inhalation routes showed no significant effects in rats; some ocular irritation was observed in the inhalation study. There were no effects on reproductive organs that were evaluated in two repeated-dose toxicity studies (one 90-day and one 14-week). In a developmental toxicity study, no effects were seen on developing fetuses up to 5000 mg/kg-bw/day. Propylene carbonate was not mutagenic in bacteria and did not induce chromosomal aberrations *in vivo*. Propylene carbonate did not increase the incidence of tumors in male mice a 2-year dermal carcinogenicity assay.

The potential health hazard of propylene carbonate is low.

No data gaps were identified for the purposes of the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

A summary of physical-chemical properties and environmental fate data submitted is provided in the Appendix. For the purpose of the screening-level hazard characterization, the review and summary of these data was limited to the octanol-water partition coefficient and biodegradation endpoints as indicators of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

Log K_{ow}: -0.41

Biodegradation:

In a Modified Sturm Test using domestic activated sludge as inoculum, 86% of the propylene carbonate had degraded after 28 days.
Propylene carbonate is readily biodegradable.

Conclusion: The Log K_{ow} of propylene carbonate indicates that its potential to bioaccumulate is expected to be low. Propylene carbonate is readily biodegradable, indicating that it is not expected to persist in the environment.

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

n-Butylene carbonate (CAS No 4437-85-8, supporting chemical)
Rainbow trout (*Salmo gairdneri*) were exposed to n-butylene carbonate at nominal concentrations of 0, 100, 180, 320, 560 and 1000 mg/L under semi-static (24-hour renewal) conditions for 96 hours. Measured concentrations were < 2.7 (limit of quantitation), 97, 162, 313 and 565 mg/L.
96-h LC_{50} = 480 mg/L

Acute Toxicity to Aquatic Invertebrates

n-Butylene carbonate (CAS No 4437-85-8, supporting chemical)
Daphnia magna were exposed to n-butylene carbonate at a nominal concentration of 1000 mg/L under static conditions for 48 hours. Measured concentrations were 910 and 964 mg/L at 0 hours and 844 and 903 at 48 hours.
48-h EC_{50} > 1000 mg/L

Toxicity to Aquatic Plants

Propylene carbonate (CAS No. 108-32-7)
Green algae (*Selenastrum capricornutum*) were exposed to propylene carbonate at nominal concentrations of 0, 62.5, 125, 250, 500 and 1000 mg/L for 96 hours. Measured concentrations at initiation were <MQL, 59.2, 120, 221, 463 and 929 mg/l; at 72 hours were <MQL, 49.8, 88.6, 181, 355 and 773 mg/l; at 96 hours were <MQL, 27.7, 56.1, 138, 331 and 740 mg/l. Only an EC_{50} for 48 hours was provided in the robust summary. Growth curves showed no differences after 72 and 96 hours of exposure. There was no statistically significant reduction in cell density, area under the growth curve, or growth rate at 96 hours.
72-h EC_{50} (growth) > 929 mg/L
96-h EC_{50} (growth) > 929 mg/L

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

3. Human Health Effects

Acute Oral Toxicity

Sprague-Dawley rats (5/sex) were administered propylene carbonate via gavage at 5000 mg/kg-bw and observed for 14 days. No mortality was seen.
LD_{50} > 5000 mg/kg-bw

Acute Dermal Toxicity

New Zealand White rabbits (5/sex) were administered propylene carbonate dermally at 3000 mg/kg-bw to abraded skin under occluded conditions for 24 hours and observed for 14 days. No mortality was seen.
LD_{50} > 3000 mg/kg-bw

Repeated-Dose Toxicity Study

(1) Sprague-Dawley rats (15/sex/dose) were administered propylene carbonate via gavage at 0, 1000, 3000 and 5000 mg/kg-bw/day, 5 days/week for 90 days. Five rats/sex/dose were sacrificed after 30 days. An additional 10 rats/sex were used as recovery groups for control and high-dose and were sacrificed 28 days post-dosing. The control group received distilled water. Hematology, clinical chemistry, ophthalmoscopy and organ weights were evaluated. Macroscopic and microscopic examinations or organs and tissues were conducted at necropsy. No treatment related effects or changes were observed during the study.
NOAEL = 5000 mg/kg-bw/day (based on no effects at the highest dose tested)

(2) F344 rats (10/sex/concentration) were exposed to propylene carbonate aerosol via inhalation at 100, 500 and 1000 mg/m^3 (0, 0.1, 0.5 and 1.0 mg/L) for 6 hours/day, 5 days/week, for 14 weeks. A neurotoxicity evaluation was conducted on 5 rats/sex/concentration. An additional 2 rats/sex (control and high dose) were evaluated for neurotoxicity following a single exposure. The control group received clean air. Hematology, clinical chemistry, ophthalmoscopy, food and water consumption, body weights, functional operation battery and motor activity were evaluated. Organ weights were taken and macroscopic and microscopic examinations were conducted. Ocular irritation and periocular swelling were seen at 0.5 and 1.0 mg/L. No treatment-related effects on any of the other parameters were observed.
LOAEL = 0.50 mg/L/day (based on ocular irritation)
NOAEL = 0.10 mg/L/day

Reproductive Toxicity

The sponsor did not submit reproductive toxicity test data. Evaluation of effects on reproductive organs in the repeated dose toxicity studies and the availability of the developmental toxicity study addressed the reproductive toxicity endpoint for the purposes of the HPV Challenge Program.

(1) In the repeated-dose toxicity study using Sprague-Dawley rats described previously, macroscopic and microscopic examinations were conducted on ovaries, uterus, testes and accessory sex organs. No effects of propylene carbonate were noted on the reproductive organs.

(2) In the repeated dose toxicity study using F344 rats described previously, macroscopic and microscopic examinations were conducted on ovaries, uterus, testes, and accessory sex organs. No effects on reproductive organs were observed.

Developmental Toxicity

Pregnant Sprague-Dawley rats (27/dose) were administered propylene carbonate via gavage at concentrations of 0, 1000, 3000 and 5000 mg/kg-bw/day on days 6 – 15 of gestation. Mortality was seen at 3000 and 5000 mg/kg-bw/day. Reduced food consumption was observed at 3000 and 5000 mg/kg-bw/day on days 6 – 13 and decreased body weight gain was observed at 5000 mg/kg-bw/day. Salivation and decreased activity in some rats were observed on days 6 – 15 at 3000 and 5000 mg/kg-bw/day. No significant abnormalities were observed in the fetuses.
LOAEL (maternal toxicity) = 3000 mg/kg-bw/day (based on clinical signs, mortality)
NOAEL (maternal toxicity) = 1000 mg/kg-bw/day
NOAEL (developmental toxicity) = 5000 mg/kg-bw/day (based on no effects at the highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro
Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to propylene carbonate at concentrations of 50, 167, 500, 1667 and 5000 μg/plate in the presence and absence of metabolic activation.
Propylene carbonate was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo
CRL CD-1 mice (15/sex) were administered propylene carbonate via intraperitoneal injection at 1666 mg/kg-bw. Five mice/sex/dose were sacrificed 30, 48 and 72 hours after injection. The number of micronucleated polychromatic erythrocytes per 1000 polychromatic erythrocytes was significantly increased ($p < 0.05$) following the 72 hour exposure. A confirmatory test was conducted that included 10 males and 10 females exposed to propylene carbonate for 72 hours only. No increase in the micronucleated polychromatic erythrocytes was seen in this test. Because positive results were obtained only at 72 hours and not confirmed in the confirmatory test with a greater number of animals, the results were considered by the study authors to be negative. Positive and negative control animals showed appropriate responses.
Propylene carbonate did not induce chromosomal aberrations in this assay.

Additional Information

Carcinogenicity

Jackson C3H/HeJ mice (50 males) were administered propylene carbonate via dermal route at 0 and 50 μl/mouse (~1500 – 2000 mg/kg-bw/dose) twice/week for 104 weeks. No increase in tumor incidence was observed.
Propylene carbonate did not increase the incidence of tumors in male mice a 2-year dermal carcinogenicity assay.

Conclusion: Acute toxicity of propylene carbonate via oral and dermal routes is low to rats and rabbits respectively. Repeated exposure via oral and inhalation routes showed no significant effects in rats; some ocular irritation was observed in the inhalation study. There were no effects on reproductive organs that were evaluated in two repeated-dose toxicity studies (one 90-day and one 14-week). In a developmental toxicity study no effects were seen on developing fetuses up to 5000 mg/kg-bw/day. Propylene carbonate was not mutagenic in bacterial cells in vitro and did not induce chromosomal aberrations in vivo. Propylene carbonate did not increase the incidence of tumors in male mice a 2-year dermal carcinogenicity assay.

The potential health hazard of propylene carbonate is low.

4. Hazard Characterization

The Log K_{ow} of propylene carbonate indicates that its potential to bioaccumulate is expected to be low. Propylene carbonate is readily biodegradable, indicating that it is not expected to persist in the environment.

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

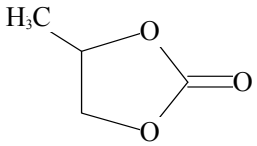
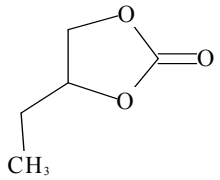
Acute toxicity of propylene carbonate via oral and dermal routes is low to rats and rabbits respectively. Repeated exposure via oral and inhalation routes showed no significant effects in rats; some ocular irritation was observed in the inhalation study. There were no effects on reproductive organs that were evaluated in two repeated-dose toxicity studies (one 90-day and one 14-week). In a developmental toxicity study no effects were seen on developing fetuses up to 5000 mg/kg-bw/day. Propylene carbonate was not mutagenic in bacterial cells in vitro and did not induce chromosomal aberrations in vivo. Propylene carbonate did not increase the incidence of tumors in male mice a 2-year dermal carcinogenicity assay.

The potential health hazard of propylene carbonate is low.

5. Data Gaps

No data gaps were identified for the purposes of 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 Propylene Carbonate (108-32-7)**	**SUPPORTING CHEMICAL n-Butylene Carbonate (4437-85-8)**
Structure		
Summary of Physical-Chemical Properties and Environmental Fate Data		
Melting Point (ºC)	-48	—*
Boiling Point (ºC)	242	—*
Vapor Pressure (hPa at 25°C)	0.059	
Log K_{ow}	-0.41	—*
Water Solubility (mg/L at 25°C)	1.75×10^3	—*
Direct Photodegradation	—	—*
Indirect (OH^-) Photodegradation Half-life ($t_{1/2}$)	4 days	—*
Stability in Water (Hydrolysis) Half-life ($t_{1/2}$)	8.97 days (at pH 7 and 35°C)	
Fugacity (Level III Model) **Air (%)** **Water(%)** **Soil (%)** **Sediment (%)**	 0.946 46.4 52.6 0.0776	—*
Biodegradation at 28 days (%)	86 Readily biodegradable	—*
Summary of Environmental Effects – Aquatic Toxicity Data		
Fish 96-h LC_{50} (mg/L)	No Data 480 (RA)	480
Aquatic Invertebrates 48-h EC_{50} (mg/L)	No Data > 1000 (RA)	> 1000
Aquatic Plants 96-h EC_{50} (mg/L)	> 929	—*

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program		
Endpoints	**SPONSORED CHEMICAL Propylene Carbonate (108-32-7)**	**SUPPORTING CHEMICAL n-Butylene Carbonate (4437-85-8)**
Summary of Human Health Data		
Acute Oral Toxicity LD_{50} (mg/kg-bw)	> 5000	—*
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	> 3000	—*
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 5000 LOAEL > 5000	—*
Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L/day)	NOAEL = 0.10 LOAEL = 0.50	—*
Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day)	Evaluation of reproductive organs from the repeated-dose toxicity studies (oral and inhalation) showed no effects.	—*
Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) **Maternal Toxicity** **Developmental Toxicity**	 LOAEL = 3000 NOAEL = 1000 NOAEL = 5000	—*
Genetic Toxicity – Gene Mutation *In vitro*	Negative	—*
Genetic Toxicity – Chromosomal Aberrations *In vivo*	Negative	—*
Additional Information – Carcinogenicity	Propylene carbonate did not increase the incidence of tumors in male mice in a 2-year dermal carcinogenicity assay.	—*

— indicates endpoint was not addressed for this chemical; * indicates data is not necessary for supporting chemical