AR201-13688

PROPYLENE CARBONATE / t-BUTYL ALCOHOL HPV COMMITTEE
1250 Connecticut Avenue, N.W., Suite 700, Washington, DC 20036
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April 10, 2002

Ms. Christie Whitman, Administrator
US Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116
Via E-mail: oppt.ncic@epa.gov and chem.rtk@epa.gov

Re: Chemical Right-to-Know HPV Challenge Program Submission

Dear Ms. Whitman:

The Propylene Carbonate / t-Butyl Alcohol HPV Committee is pleased to submit the attached test plans and robust summaries for propylene carbonate (CAS RN 108-32-7) and t-butyl alcohol (CAS RN 75-65-0) under the HPV Challenge Program, AR-201. The Committee is submitting this information directly to directly to EPA with the understanding that a 120-day review period for public comment will follow this submission. The test plan and robust summaries for each chemical are being submitted in electronic format as PDF files.

If you have any questions, please do not hesitate to contact me.

Sincerely,

Robert J. Fensterheim
Executive Director

Test Plan
for

Propylene Carbonate

CAS Number 108-32-7

USEPA HPV Challenge Program Submission

April 10, 2002

Submitted by:

Propylene Carbonate / t-Butyl Alcohol HPV Committee

Members:

Lyondell Chemical Company
Huntsman Corporation

Prepared by:
ToxWorks
1153 Roadstown Road
Bridgeton, New Jersey 08302-6640
Phone: 856-453-3478

I. Introduction

The Propylene Carbonate / t-Butyl Alcohol HPV Committee and its member companies have committed voluntarily to develop screening level human health effects, environmental fate and effects, and physicochemical test data for propylene carbonate under the Environmental Protection Agency's High Production Volume Challenge Program.

Propylene Carbonate (PC) is produced in a continuous process by the reaction of propylene oxide (PO) with CO_2 and sold as different purity and color grades dependent on the supplier. PC may be used as a solvent for chemical reactions or as a carrier of cosmetically active agents, medicinal agents, biocides, and fungicides. PC may also be used as a reactive intermediate in alkoxylations, transesterifications, polymerizations, reaction with amines, or carboxylic acids. PC is a popular solvent for lithium ion batteries. It is used in the production of electrochromic or "auto-dimming" mirrors for automobiles.

Data Summary

	Data Available	Data Adequate	testing recommended
Melting point	Yes	Yes	No
Boiling point	Yes	Yes	No
Vapor Pressure	Yes	Yes	No
Partition Coefficient	Yes	Yes	No
Water Solubility	Yes	Yes	No
Stability in Water	No	No	Yes
Transport	No	No	Yes
Photodegradation	Yes	Yes	No
Biodegradation	Yes	Yes	No
Acute Toxicity to Fish	Yes	Yes	No
Acute Toxicity to Invert.	Yes	Yes	No
Acute Toxicity to aq.plants	No	No	Yes
Acute Tox – oral	Yes	Yes	No
Acute Tox – dermal	Yes	Yes	No
Gene Tox *in vivo* – MN	Yes	Yes	No
Gene Tox *in vitro* – Ames	Yes	Yes	No
Repeat dose- oral (90 day)	Yes	Yes	No
Repeat dose-inhal (90 day)	Yes	Yes	No
Repeat dose-derm (2 year)	Yes	Yes	No
Reproductive toxicity	Limited	Yes	No
Developmental tox	Yes	Yes	No

II. Test Plan and Rationale

A. Physical Chemical Data

The physical /chemical data for propylene carbonate are found in standard reference works. The underlying data were not found, but additional testing is not justified. Data on the stability of propylene carbonate in water and transport between environmental compartments are not adequate. **Recommended testing:**

1. Stability in Water: OECD Test Guideline 111

   Propylene carbonate may hydrolyze under some conditions; therefore, its stability in water under various pH conditions should be determined.

2. Transport and Distribution between Environmental Compartments: Level 1 EQC Model

   The US EPA has acknowledged that computer modeling techniques are an appropriate method for estimating chemical partitioning among environmental compartments. A widely used fugacity model is the Equilibrium Criterion Model (EQC; Mackay et al., 1996). EPA has indicated that it accepts Level I fugacity data as an estimate of chemical distribution values. In EQC level I, distribution is calculated as percent partitioned to 6 compartments within a unit world. Level I data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical is likely to partition.

B. ECOTOXICITY

Acute toxicity studies on fish and daphnia on a propylene carbonate analog, butylene carbonate, were conducted according to OECD Guidelines, following GLP guidelines. Butylene carbonate (CAS # 4437-85-8) is considered an acceptable surrogate for propylene carbonate because of similar physical-chemical properties.

In rainbow trout the LC50 for butylene carbonate was 480 mg/l and in Daphnia the EC50 was >1000 mg/l. Based on similarity to butylene carbonate, propylene carbonate is not expected to be significantly more toxic to aquatic organisms. The low toxicity of butylene carbonate provides adequate information to conclude that propylene carbonate is not likely to be more than slightly toxic to aquatic organisms. Additional testing of propylene carbonate is not needed.

A biodegradation study of propylene carbonate was published in German in Git. Fachz. Lab. Based on the English abstract, propylene carbonate is readily biodegradable; more than 80% biodegraded during 10 days. Additional biodegradation data are not needed.

Recommended ecotoxicity testing: Toxicity to Aquatic plants (*e.g.*, Algae): OECD Test Guideline 201

No studies of propylene carbonate toxicity to algae are available; an acute toxicity study in algae is recommended (OECD guideline).

C. MAMMALIAN TOXICITY

Numerous adequate and reliable acute toxicity tests are available on propylene carbonate. Oral and dermal tests meet OECD and EPA test guidelines. Propylene carbonate is practically nontoxic following acute exposures; the oral LD50 is >5000 mg/kg and the dermal LD50 is >3000 mg/kg. No further testing is recommended.

Subchronic studies (13-14 weeks) of propylene carbonate by inhalation (aerosol) and oral (gavage) routes were conducted in rats according to current guidelines. The oral study indicated low systemic toxicity from propylene carbonate (NOAEL = 5000 mg/kg/day). In the inhalation study, no systemic toxicity was seen at concentrations up to 1000 mg/m^3; however, there was periocular irritation and swelling in a few males at 500 and 1000 mg/m^3. A dermal carcinogenicity study in mice did not indicate tumorigenic potential or systemic toxicity from 2 years of exposure to propylene carbonate. No further testing is recommended.

There is a negative Ames *in vitro* mutagenicity assay of propylene carbonate. A single intraperitoneal injection of 1666 mg/kg propylene carbonate did not induce an increase in micronuclei when examined after 30, 48 and 72 hours. The mutagenicity battery is satisfactorily filled; no further mutagenicity testing is recommended.

Gavage administration of propylene carbonate to pregnant rats days 6-15 of gestation resulted in systemic toxicity at doses of 3000 and 5000 mg/kg/day, including mortality (not seen in 13 week study of non-pregnant rats). The NOAEL for maternal toxicity was 1000 mg/kg/day. This indicates that pregnant rats are more susceptible to propylene carbonate than are non-pregnant rats. There were no significant differences in live litter size, average fetal weight, percentage of males, or malformed fetuses. No further developmental toxicity testing is recommended.

No studies of the effect of propylene carbonate on reproduction are available. However, no adverse effects on testis, ovaries, or accessory sex organs were noted in rats following oral or inhalation of propylene carbonate for 13 weeks. Therefore, reproductive effects from propylene carbonate are unlikely and further testing is not recommended.

Robust Summaries
for

Propylene Carbonate

CAS Number 108-32-7

USEPA HPV Challenge Program Submission

April 10, 2002

Submitted by:

Propylene Carbonate / t-Butyl Alcohol HPV Committee

Members:

Lyondell Chemical Company
Huntsman Corporation

Prepared by:
ToxWorks
1153 Roadstown Road
Bridgeton, New Jersey 08302-6640
Phone: 856-453-3478

Propylene Carbonate
High Production Volume
Robust Summaries of Existing Studies

PHYSICAL/CHEMICAL ELEMENTS

Data Point	Method	Value
1) MELTING POINT	Not Stated	-48.8 °C

Reference: Lide, D.R. (ed.). CRC Handbook of Chemistry and Physics. 79th ed. Boca Raton, FL: CRC Press Inc. 1998-1999, p. 3-145.

2) BOILING POINT	Not Stated	242 °C

Reference: Lide, D.R. (ed.). CRC Handbook of Chemistry and Physics. 79th ed. Boca Raton, FL: CRC Press Inc. 1998-1999, p. 3-145.

3) VAPOUR PRESSURE	Not Stated	0.045 mm Hg

Reference: Daubert, T.E., Danner, R.P. Physical and Thermodynamic Properties of Pure Chemicals Data Compilation. Washington, DC, Taylor and Francis, 1989.

4) PARTITION COEFFICIENT Not stated Log Pow: -0.41 Temp: Not stated

Reference: Hansch, C., Leo., A., Hoekman, D., 1995. Exploring QSAR – Hydrophobic, Electronic, and Steric Constants. Washington, DC, American Chemical Society, p. 9.

5) WATER SOLUBILITY	Not Stated	175,000 mg/l @ 25 °C

Reference: Riddick, J.A., Bunger, W.B., Sakano, T.K., 1985. Techniques of Chemistry 4th ed., Volume II. Organic Solvents. New York, NY, John Wiley and Sons, p. 434.

6) PHOTODEGRADATION Calculated Half-life t 1 2 (preferred): 4 days

Sensitizer (type) – hydroxyl radicals Rate Constant : 4.7x10-12 cu cm/molecule-sec @ 25 °C

Reference: Meylan, W.M., Howard, P.H., 1993. Chemosphere 26: 2293-2299.

9) BIODEGRADATION

TEST SUBSTANCE

Identity: Propylene carbonate

METHOD

Method/guideline followed: Manostatic respirometer screening study
Test Type (test type/aerobic/anaerobic): Aerobic
GLP (Y/N): No data
Year (study performed): Not stated
Contact time (units): 10 days
Innoculum: Seed from wastewater treatment plant
Remarks field for Test Conditions:

- Concentration of test chemical, vehicle used, pre-acclimation conditions: Not stated
- Temperature of incubation °C: Not stated
- Dosing procedure: Not stated
- Sampling frequency: Not stated
- Appropriate controls and blank system used? Not stated
- Analytical method used to measure biodegradation: Not stated
- Method of calculating measured concentrations (i.e., arithmetic mean, geometric mean, etc.): Not stated

RESULTS

Degradation % after time: 80 % during a 10-day period
- For each time period %: Not stated

Breakdown products (yes/no) If yes describe breakdown products and whether they were transient or stable in the Remarks field for Results. Not stated

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: Submitter concludes that propylene carbonate is readily biodegradable.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 2, key study
Remarks field for Data Reliability: Not standard test; limited details available

REFERENCES (Free Text)

Kayser, G et al., 1993. Git Fachz Lab 37: 416-419

OTHER

Last changed (administrative field for updating): 3/11/02 by ToxWorks

ECOTOXICITY ELEMENTS

10) ACUTE TOXICITY TO FISH

TEST SUBSTANCE

Identity : n-Butylene carbonate
Remarks field for Test Substance: analog of Propylene carbonate

METHOD

Method/guideline followed (experimental/calculated): OECD 203

Type (test type): Semistatic, daily renewal
GLP (Y/N): Yes
Year (study performed): 1988
Species/Strain/Supplier: Rainbow trout (*Salmo gairdneri*), Parkwood Trout Farm, Kent, UK
Analytical monitoring: Yes
Exposure period (unit): 96 hours
Statistical methods: Thompson and Weil, 1952. Biometrics 8: 51-54.
Remarks field for Test Conditions:
- Test fish (Age/length/weight, loading, pretreatment) - Test conditions, e.g.: age- not given, length – 6.4±0.3 cm, weight- 3.96±0.8 g, acclimated to lab 17 days, acclimated to test conditions 7 days
· Details of test (static, semi-static, flow-through): Daily renewal
· Dilution water source: Laboratory tap water, dechlorinated
· Dilution water chemistry (hardness, alkalinity, pH, TOC, TSS, salinity): hardness – 350 mg/l as $CaCO_3$,
· Stock and test solution and how they are prepared: 100, 180, 320, 560, and 1000 mg/l– direct dispersion into water
· Stability of the test chemical solutions: Verified by chemical analysis
· Exposure vessel type (e.g., size, headspace, sealed, aeration, lighting, # per treatment): Glass aquaria holding 40 l of test media
· Number of replicates, fish per replicate: 1 replicate of 10 fish per concentration
· Water chemistry in test (D.O., pH) in the control and one concentration where effects were observed: DO = 9.6 – 10.1 in control; 9.5 – 10.1 in treatment groups; pH7.8 –7.9
- Test temperature range - Method of calculating mean measured concentrations (i.e. arithmetic mean, geometric mean, etc.): 14.0 °C at all measurement times

RESULTS

Nominal concentrations (as mg/L): 0, 100, 180, 320, 560, 1000
Measured concentrations (as mg/L): <2.7 (loq), 103, 150, 318, 534, 875 at 0 hrs
<2.7 (loq), 99, 167, 338, 524, 907 at 24 hrs
<2.7 (loq), 97, 162, 313, 565 at 96 hrs
Element value (e.g. LC50, LCo, LL50, or LL0 at 48, 72 and 96 hours, etc., based on measured or nominal concentrations): LC50 at 48 = 510 (410-620), 72 = 480 (400-580), and 96 = 480 (400-580) mg/l based on nominal concentration.
Remarks field for Results:
- Biological observations: Hyperactive, swimming at surface, increased pigmentation, loss of equilibrium
- Table showing cumulative mortality:

(mg/l)	hours: 6	24	48	72	96
control	0	0	0	0	0
100	0	0	0	0	0
180	0	0	0	0	0
320	0	0	0	0	0
560	1	2	7	8	8
1000	4	10	10	10	10

- Lowest test substance concentration causing 100% mortality: 1000 mg/l
- Mortality of controls: 0
- Reference substances (if used) - results: None used

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: Submitter concludes low acute toxicity to fish from butylene carbonate and therefore also expected for propylene carbonate.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1, key study

REFERENCES (Free Text)

Douglas, M.T., Sewell, I.A., Macdonald, I.A., 1989. The Acute toxicity of n-Butylene carbonate to rainbow trout (Salmo gairdneri). Huntingdon Life Sciences Report TXO 11 (c) /89488, pp. 1-14.

OTHER

Last changed (administrative field for updating): 3/11/02 by ToxWorks

12) ACUTE TOXICITY TO AQUATIC INVERTEBRATES (E.G., DAPHNIA)

TEST SUBSTANCE

Identity: n-Butyl carbonate
Remarks field for Test Substance: Analog of propylene carbonate

METHOD

Method/guideline followed (experimental/calculated): OECD 202 Part 1
Test type: Acute toxicity (immobilization)
GLP (Y/N): Yes
Year (study performed): 1988
Analytical procedures: Yes
Species/Strain: Daphnia magna (Straus)
Test details (static, semi-static, dosing rate, flow-through rate, etc.): Static
Statistical methods: No
Remarks field for Test Conditions:
- Test organisms:
· source, supplier, any pretreatment, breeding method: Laboratory culture derived from strain supplied by IRCHA in France. Reproduction by parthenogenesis
· Age at study initiation: less than 24 hours

· Control group: Yes
- Test conditions:
· Stock solutions preparation (vehicle, solvent, concentrations) and stability: Direct dispersion at 1000 mg/l
· Test temperature range: 22.0 °C
· Exposure vessel type (e.g., size, headspace, sealed, aeration, # per treatment): Glass jars containing 200 ml of test solution
· Dilution water source: Dechlorinated tap water
· Dilution water chemistry (hardness, alkalinity, pH, TOC, TSS, salinity, Ca/Mg ratio, Na/K ratio): 350 mg/l as $CaCO_3$, pH 8.
· Lighting (quality, intensity and periodicity): 16 hrs light/8 dark
· Water chemistry in test (D.O., pH) in the control and at least one concentration where effects were observed: DO = 9.4 – 9.8 mg/l, pH – 8.
- Element (unit) basis (i.e. immobilization): Immobilization
- Test design (number of replicates, individuals per replicate, concentrations): 4 replicates of 10 organisms in control and treated groups
- Method of calculating mean measured concentrations (i.e. arithmetic mean, geometric mean, etc.): Not stated
- Exposure period : 48 hours
- Analytical monitoring : Yes

RESULTS

Nominal concentrations in mg/L: 1000 mg/l
Measured concentrations in mg/L: 910 and 964 at 0 hrs; 844 and 903 at 48 hrs
Unit [results expressed in what unit]: mg/l
EC50, EL50, LC0, LL0, at 24, 48 hours: >1000 mg/l
Statistical results, as appropriate
Remarks field for Results:
- Biological observations:
· Number immobilized as compared to the number exposed: No effects
· Cumulative immobilization: Zero

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: Submitter concludes low acute toxicity to daphnia from butylene carbonate and therefore also expected for propylene carbonate.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1, key study

REFERENCES (Free Text)

Douglas, M.T., Sewell, I.A., Macdonald, I.A., 1989. The Acute toxicity of n-Butylene carbonate to Daphnia magna. Huntingdon Life Sciences Report TXO 11 (b) /89505, pp. 1 - 13.

OTHER

Last changed (administrative field for updating): 3/11/02 by ToxWorks

HEALTH ELEMENTS

13a) ACUTE TOXICITY

TEST SUBSTANCE

Identity: Propylene carbonate

METHOD

Method/guideline followed (experimental/calculated): equivalent to EPA 870.1100
Type (test type): Acute lethality
GLP (Y/N): Yes
Year (study performed): 1985
Species/Strain: Sprague-Dawley rats
Sex: Both
No. of animals per sex per dose: 5
Vehicle: None
Route of administration (if inhalation - aerosol, vapor, gas, particulate): Oral
Remarks field for Test Conditions:
- Age (Not reported) – Weight 180-219 g after fasting.
- Doses (OECD guidelines 401 and 425 do not provide dose levels, so these must be described in detail) – 5000 mg/kg
- Doses per time period – One dose
- Volume administered or concentration: As received
- Post dose observation period: 14 days

RESULTS

Value [LD50 or LC50] with confidence limits if calculated: >5000 mg/kg
Number of deaths at each dose level: None
Remarks field for Results:
- Description, severity, time of onset and duration of clinical signs at each dose level: No clinical signs
- Necropsy findings, included doses affected, severity and number of animals affected: No abnormalities in any animal

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter. Submitter concludes that propylene carbonate is practically non-toxic from acute oral exposure.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1; key study

REFERENCES (Free Text)

Mallory, V.T., Naismith, R.W., Matthews, R.J., 1985. Acute Oral Toxicity Study in Rats (14 day), Pharmakon Research International Final Report PH 402-TX-004-85, pp. 1-13.

OTHER

Last changed (administrative field for updating): 11/21/01 by ToxWorks

13b) ACUTE TOXICITY

TEST SUBSTANCE

Identity: Propylene carbonate

METHOD

Method/guideline followed (experimental/calculated): Equivalent to EPA 870.1200
Type (test type): Acute lethality
GLP (Y/N): Yes
Year (study performed): 1986
Species/Strain: New Zealand White Rabbits
Sex: Both
No. of animals per sex per dose: 5
Vehicle: None
Route of administration (if inhalation - aerosol, vapor, gas, particulate): Dermal
Remarks field for Test Conditions:
- Age (Not reported) – Weight 2-3 kg.
- Doses (OECD guidelines 401 and 425 do not provide dose levels, so these must be described in detail) – 3000 mg/kg applied to abraded skin and occluded for 24 hours.
- Doses per time period – One dose
- Volume administered or concentration: As received
- Post dose observation period: 14 days

RESULTS

Value [LD50 or LC50] with confidence limits if calculated: >3000 mg/kg

Number of deaths at each dose level: None
Remarks field for Results:
- Description, severity, time of onset and duration of clinical signs at each dose level:
  No clinical signs
- Necropsy findings, included doses affected, severity and number of animals affected:
  No abnormalities in any animal

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter. Submitter concludes that propylene carbonate is practically non-toxic following a single dermal exposure.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1

REFERENCES (Free Text)

Mallory, V.T., Matthews, R.J., 1986. Acute Dermal Toxicity Test in Rabbits (14 day), Pharmakon Research International Final Report PH 422-TX-006-86, pp. 1-15.

OTHER

Last changed (administrative field for updating): 9/10/01 by ToxWorks

GENETIC TOXICITY ELEMENTS

14) GENETIC TOXICITY IN VIVO (CHROMOSOMAL ABERRATIONS)

TEST SUBSTANCE

Identity: Propylene carbonate

METHOD

Method/guideline followed: Equivalent to EPA 870-5395
Type (test type): Micronucleus in mice
GLP (Y/N): Yes
Year (study performed): 1985
Species: Mouse
Strain: CRL CD-1
Sex: Both
Route of administration (if inhalation - aerosol, vapor, gas, particulate): Intraperitoneal injection
Doses/concentration levels: 1666 mg/kg

Exposure period: Single injection; subgroups were exposed for 30, 48 and 72 hours
Statistical methods: One-tailed t-test
Remarks field for Test Conditions:
- Age at study initiation: Seven and one-half weeks
- No. of animals per dose: 15 males and 15 females (5 for each time point): retest including 10 male and 10 female exposed for 72 hours only
- Vehicle: Distilled water
- Duration of test: 72 hours
- Frequency of treatment : Once
- Sampling times and number of samples: 30, 48, and 72 hours
- Control groups and treatment: Untreated control, positive control (TEM), one dose level of test material
- Clinical observations performed (clinical pathology, functional observations, etc.): Toxic signs
- Organs examined at necropsy (macroscopic and microscopic): Not stated
- Criteria for evaluating results (for example, cell types examined, number of cells counted in a mouse micronucleus test): 1000 PCEs
- Criteria for selection of M.T.D.: Highest non-lethal dose in preliminary test

RESULTS

Effect on mitotic index or PCE/NCE ratio by dose level by sex:

	MN/1000 PCE	PCE/NCE
H2O	0.20±0.42	1.61±0.55
TEM	54.23±16.78*	0.77±0.18*
PC-30 hr	0.50±0.97	1.76±0.42
PC-48 hr	0.30±0.48	1.43±0.50
PC-72 hr	1.20±1.40*	1.59±.037
Repeat		
H2O	0.50±0.85	1.92±0.48
TEM	48.5±9.03*	0.83±0.20*
PC-72 hr	0.30±0.57	1.77±.064

Genotoxic effects (positive, negative, unconfirmed, dose-response, equivocal): Negative
NOAEL(NOEL) (C)/LOAEL(LOEL) (C)
Statistical results, as appropriate: * = statistically significant at $p < 0.05$
Remarks field for Results: Because positive result obtained only at 72 hours and not confirmed in repeat test with larger animal population (10/sex instead of 5/sex), the authors judged the results to be negative.
- Mortality at each dose level by sex: None
- Mutant/aberration/mPCE/polyploidy frequency, as appropriate: See table above
- Description, severity, time of onset and duration of clinical signs at each dose level and sex: Writhing after dosing; decreased body tone in some animals
- Body weight changes by dose and sex: No significant changes
- Food/water consumption changes by dose and sex: Not recorded

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: The authors concluded the study was negative.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1; key study

REFERENCES (Free Text)

Sorg, R.M., Naismith, R.W., Matthews, R.J., 1986. Micronucleus Test (MNT) – OECD, Pharmakon Research International, Inc. Final Report PH 309A-TX-004-85, pp. 1-58.

OTHER

Last changed (administrative field for updating): 3/11/02 by ToxWorks

15) GENETIC TOXICITY IN VITRO (GENE MUTATIONS)

TEST SUBSTANCE

Identity: Propylene carbonate

METHOD

Method/guideline followed: Ames method, equivalent to EPA 870-5100 except did not test *E.coli*.
Type (e.g. reverse mutation assay, gene mutation study, cytogenetic assay, mammalian cell gene mutation assay, cytogenetic assay, etc.): Reverse mutation - Ames
System of testing [bacterial, non bacterial]: Bacterial
GLP (Y/N): Yes
Year (study performed): 1985
Species/Strain or cell type and or cell line, bacterial or non-bacterial: Salmonella, TA98, TA100, TA 1535, TA1537, TA1538
Metabolic activation: S-9 from liver of Sprague-Dawley rats treated with Aroclor 1254
- Species and cell type
- Quantity
- Induced or not induced
Concentrations tested: 50, 167, 500, 1667, and 5000 ug/plate as preincubation assay
Statistical Methods: Moore and Felton, 1983. Mutat. Res. 119: 95-102.
Remarks field for Test Conditions:
- Test Design
· Number of replicates: Three

· Frequency of Dosing: Pre-incubation assay
- Criteria for evaluating results (e.g. cell evaluated per dose group): triple untreated control rate or statistically significant trend

RESULTS

Result:
Cytotoxic concentration:
- With metabolic activation: >5000 µg/plate
- Without metabolic activation: >5000 µg/plate
Genotoxic effects (e.g. positive, negative, unconfirmed, dose-response, equivocal):
- With metabolic activation: Negative
- Without metabolic activation: Negative
Statistical results, as appropriate:

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: The authors concluded that the test material was negative in the Ames assay.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1, key study

REFERENCES (Free Text)

Godek, E.G., Naismith, R.W., Matthews, R. J., 1985. Ames Salmonella/Microsome Liquid Pre-Incubation Assay. Pharmakon Research International Inc Final Report PH 301-TX-006-85, pp. 1-22.

OTHER

Last changed (administrative field for updating): 9/14/01 by ToxWorks

16a) REPEATED DOSE TOXICITY

TEST SUBSTANCE

Identity: Propylene carbonate

METHOD

Method/guideline followed: Equivalent to OECD 408
Test type: 90 day Oral Study
GLP (Y/N): Yes
Year (study performed): 1988

Species: Rat
Strain: Charles River Sprague-Dawley derived
Route of administration, oral (gavage, drinking water, feed), dermal, inhalation (aerosol, vapor, gas, particulate), other: Gavage
Duration of test : 90 Days
Doses/concentration levels: 0, 1000, 3000, 5000 mg/kg/day
Sex: Both
Exposure period: 90 days
Frequency of treatment: Five days/week for 13 weeks
Control group and treatment : Distilled water by gavage
Post exposure observation period: Additional groups of control and high-dose observed for 28 days post dosing.
Statistical methods: One-way analysis of variance, followed by Dunnett's or Tukey's tests.
Remarks field for Test Conditions:
- Test Subjects:
· Age at study initiation: 40 days
· No. of animals per sex per dose - Study Design: 10, additional 5/sex/dose terminated after 30 days; additional 10/sex for control and high dose held 28 days post dosing.
· Vehicle: None, dosed as received.
· Satellite groups and reasons they were added: Control and high-dose for recovery.
· Clinical observations performed and frequency (clinical pathology, functional observations, etc.): Daily observations, hematology (RBC, Hemat., PCV, WBC, diff., plt) and clinical chemistry (glu, crea, tbil, bun, ALT, AST, GGT, Tpro, alb, glob, Na, K, Cl, Ca, P) at 30 and 90 days. Ophthalmoscopy pretest at 30 and 90 days.
· Organs examined at necropsy (macroscopic and microscopic): brain, pituitary, thyroid, parathyroid, thymus, lungs, trachea, heart, sternum with bone marrow, salivary glands, liver, spleen, kidneys, adrenals, pancreas, gonads, uterus, accessory sex organs, aorta, skin, esophagus, nasal turbinates, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, urinary bladder, lymph node, mammary gland, skeletal muscle, peripheral nerve, three levels of spinal cord, lachrymal glands.

RESULTS

NOAEL (NOEL): 5000 mg/kg/day
LOAEL (LOEL)
Actual dose received by dose level by sex, if known,
Toxic response/effects by dose level: No adverse effects seen
Statistical results, as appropriate:
Remarks field for Results:
- Body weight: No treatment effect
- Food/water consumption: No treatment effect
- Description, severity, time of onset and duration of clinical signs: No treatment effect
- Ophthalmologic findings incidence and severity: No treatment effect
- Hematological findings incidence and severity: No treatment effect
- Clinical biochemistry findings incidence and severity: Few clinical chemistry significant differences, not consistent between sexes or 30 vs. 90 days

- Mortality and time to death: No treatment effect
- Gross pathology incidence and severity: No treatment effect
- Organ weight changes: Few organ weight differences, not consistent between sexes or 30 vs 90 days
- Histopathology incidence and severity: No treatment effect

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: Authors concluded there were no treatment-related effects.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1, key study

REFERENCES (Free Text)

Margitich, D.J., 1989. Subchronic Oral toxicity in Rats. Pharmakon Research International, Inc. Final Report Ph 470-TX-001-88, pp. 1 – 158, plus two appendices.

OTHER

Last changed (administrative field for updating): 3/11/02 by ToxWorks

16b) REPEATED DOSE TOXICITY

TEST SUBSTANCE

Identity: Propylene carbonate

METHOD

Method/guideline followed: Equivalent to OECD 408
Test type: 14 Week Aerosol Inhalation Study
GLP (Y/N): Yes
Year (study performed): 1991
Species: Rat
Strain: Harlan F344
Route of administration, oral (gavage, drinking water, feed), dermal, inhalation (aerosol, vapor, gas, particulate), other: Aerosol inhalation
Duration of test : 93 Days
Doses/concentration levels: 0, 100, 500, 1000 mg/m^3; diameter (MMAD) = 4.9 microns +/- 2.5 gsd
Sex: Both
Exposure period: 93 days
Frequency of treatment: Six hours/day five days/week for 13 weeks

Control group and treatment : Clean air
Post exposure observation period: No
Statistical methods: One-way analysis of variance, followed by Dunnett's or Tukey's tests.
Remarks field for Test Conditions:
- Test Subjects:
· Age at study initiation: 47 days
· No. of animals per sex per dose - Study Design: 10, additional 5/sex/dose for neurotoxicity evaluation; additional 2/sex for control and high dose for neurotoxicity evaluation after a single exposure.
· Vehicle: None
· Satellite groups and reasons they were added: Control and high dose for neurotoxicity evaluation after a single exposure.
· Clinical observations performed and frequency (clinical pathology, functional observations, etc.): Daily observations, hematology (RBC, Hemat., PCV, WBC, diff., plt) and clinical chemistry (glu, crea, tbil, cbil, ubil, bun, ALT, AST, GGT, SDH, ALK, Tpro, alb, glob, Na, K, Cl, Ca, P) at 90 days. Ophthalmoscopy pretest and 90 days, food and water consumption first 4 weeks, body weights weekly. FOB and motor activity after six and thirteen weeks. FOB one and 23 hours after single 6-hour exposure. For FOB, animals were placed in clean clear cage for 2 minutes while observed for horizontal and vertical movement, convulsions, tremors, stereotypy, piloerection, respiration, urination, gait, and acoustic startle response. The animal was removed and observed for pupil size and response to light, vocalization, salivation, mouthbreathing, lacrimation, diarrhea, visual placing and muscle tone. Catatonia, forelimb and hindlimb grip strength, surface and air righting reflexes performance on a rotating treadmill, positive geotropism, toe and tail withdrawal reflexes, hind leg splay, and rectal temperature were recorded using simple equipment. Motor activity was determined using San Diego Instruments test equipment.
· Organs examined at necropsy (macroscopic and microscopic): brain, pituitary, thyroid, parathyroid, thymus, lungs, trachea, esophagus, nasopharyngeal tissues, larynx, heart, sternum with bone marrow, salivary glands, liver, spleen, kidneys, adrenals, pancreas, gonads, uterus, accessory sex organs, aorta, skin, nasal turbinates, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, urinary bladder, lymph node, mammary gland, skeletal muscle, peripheral nerve, three levels of spinal cord, lachrymal glands, Zymbal's glands.

RESULTS

NOAEL (NOEL): 100 mg/m^3
LOAEL (LOEL)
Actual dose received by dose level by sex, if known,
Toxic response/effects by dose level: Inflammation of ocular tissues in 2 males at 500 and 4 males at 1000 mg/m^3.
Statistical results, as appropriate:
Remarks field for Results:
- Body weight: No treatment effect
- Food/water consumption: No treatment effect

- Description, severity, time of onset and duration of clinical signs: Periocular swelling at 500 and 1000 mg/m^3
- Ophthalmologic findings incidence and severity: No treatment effect
- Hematological findings incidence and severity: No treatment effect
- Clinical biochemistry findings incidence and severity: No treatment effect
- Mortality and time to death: No treatment effect
- Gross pathology incidence and severity: No treatment effect
- Organ weight changes: Few organ weight differences, not consistent between sexes or supported by histopathologic findings.
- Histopathology incidence and severity: No treatment effect

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: Authors concluded there was mild eye irritation at 500 and 1000 mg/m^3.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1, key study

REFERENCES (Free Text)

Burleigh-Flayer, H.D., Nachreiner, D.J., Kintigh, W.J., 1991. Propylene carbonate: Fourteen-Week aerosol inhalation study on rats with neurotoxicity evaluation. Bushy Run Research Center Final Report 52-637, pp. 1 – 56, plus 12 appendices.

OTHER

Last changed (administrative field for updating): 3/07/02 by ToxWorks

16c) REPEATED DOSE TOXICITY

TEST SUBSTANCE

Identity: Propylene carbonate

METHOD

Method/guideline followed:
Test type: Dermal Carcinogenicity Study
GLP (Y/N): Yes
Year (study performed): 1987-1991
Species: Mouse
Strain: Jackson C3H/HeJ
Route of administration, oral (gavage, drinking water, feed), dermal, inhalation (aerosol, vapor, gas, particulate), other: dermal

Duration of test : 104 weeks
Doses/concentration levels: 0, 50 µl/mouse twice/week (~1500-2000 mg/kg/dose)
Sex: Male
Exposure period: 104 weeks
Frequency of treatment: Twice/week for 104 weeks
Control group and treatment : No treatment
Post exposure observation period: No
Statistical methods: One-way analysis of variance.
Remarks field for Test Conditions:
- Test Subjects:
· Age at study initiation: 8 weeks
· No. of animals per sex per dose: 50 males only
· Vehicle: None
· Satellite groups and reasons they were added: None
· Clinical observations performed and frequency (clinical pathology, functional observations, etc.): Daily observations, body weights weekly.
· Organs examined at necropsy (macroscopic and microscopic): Necropsy: Carcass and muscular/skeletal systems, external surfaces and orifices, cranial cavity and brain, neck and associated organs, thoracic, abdominal and pelvic cavities and organs. Microscopic Examination: Skin, nodules, masses and lesions.

RESULTS

NOAEL (NOEL): 1500-2000 mg/kg (twice/week)
LOAEL (LOEL)
Actual dose received by dose level by sex, if known,
Toxic response/effects by dose level: None reported
Statistical results, as appropriate:
Remarks field for Results:
- Body weight: No treatment effect
- Food/water consumption: Not measured
- Description, severity, time of onset and duration of clinical signs: No treatment effect
- Ophthalmologic findings incidence and severity: Not measured
- Hematological findings incidence and severity: Not measured
- Clinical biochemistry findings incidence and severity: Not measured
- Mortality and time to death: No treatment effect
- Gross pathology incidence and severity: No treatment effect
- Organ weight changes: Not measured
- Histopathology incidence and severity: No treatment effect

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: Authors concluded there was no increase in tumors.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1, Key study

REFERENCES (Free Text)

Garman, R.H., Van Miller, J.P., Negley, J.E., 1991. Chronic Dermal Carcinogenicity Studies in C3H/HeJ Male Mice. Bushy Run Research Center Final Report 52-527, pp. 1–143, plus 8 appendices.

OTHER

Last changed (administrative field for updating): 9/11/01 by ToxWorks

17) TOXICITY TO REPRODUCTION

TEST SUBSTANCE

Identity: Propylene Carbonate

METHOD

Method/guideline followed: Assessment of reproductive organs in a 90 day study
Type (one generation, two generation, etc.): 90 Day Oral, Evaluation of Sex organs
GLP (Y/N): Yes
Year (study performed): 1988
Species: Rat
Strain: Charles River Sprague-Dawley derived
Route of administration - oral (gavage, drinking water, feed), dermal, inhalation (aerosol, vapor, gas, particulate), other: Gavage
Doses/concentration levels: 0, 1000, 3000, 5000 mg/kg/day
Sex: Both
Control group and treatment: Yes
Frequency of treatment: Five days/week
Duration of test: 13 weeks
Premating exposure period for males (P and F1) as appropriate
Premating exposure period for females (P and F1) as appropriate
Statistical methods: One-way analysis of variance, followed by Dunnett's or Tukey's tests.
Remarks field for Test Conditions:
- Test animals:
· Number, age, sex per dose for P, F1 and F2, if appropriate: 10/sex/group at 40 days old
- Test design:
· Vehicle: None
· Dosing schedules and pre and post dosing observations periods for P, F1 and F2, if appropriate: Five days/week
- Parameters assessed during study P and F1 as appropriate:

· Clinical observations performed and frequency (clinical pathology, functional observations, etc.): Daily observations, hematology. Clinical chemistry at 30 and 90 days
· Estrous cycle length and pattern (number of days spent in each phase): Not assessed
· Sperm examination (epididymal or vas sperm, concentration, motility, morphology): Not assessed
- Parameters assessed during study F1 and F2, as appropriate:
· Clinical observations performed and frequency (weight gain, growth rate, etc.): Weekly BW
· Organs examined at necropsy (macroscopic and microscopic): Ovaries, uterus, testes, accessory sex organs

RESULTS

NOAEL (NOEL) and LOAEL (LOEL) for P, F1 and F2, as appropriate: 5000 mg/kg/day
Actual dose received by dose level by sex if known
Statistical results, as appropriate
Remarks field for Results: Assessment of reproductive organs from 90 day study
- Body weight: No treatment effect
- Food/water consumption: No treatment effect
- Description, severity, time of onset and duration of clinical signs: No treatment effect
- Hematological findings incidence and severity: No treatment effect
- Clinical biochemistry findings incidence and severity: No treatment effect
- Mortality: No treatment effect
- Gross pathology incidence and severity: No treatment effect
- Organ weight changes: No treatment effect
· Histopathology incidence and severity: No effect on ovaries, testes or accessory sex organs

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: The submitter concludes that propylene carbonate had no effect on reproductive organs

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 2, key study
Remarks field for Data Reliability: Not a guideline study of reproductive effects, but indicates no effects would be expected.

REFERENCES (Free Text)

Margitich, D.J., 1989. Subchronic Oral toxicity in Rats. Pharmakon Research International, Inc. Final Report Ph 470-TX-001-88, pp. 1 – 158, plus two appendices.

OTHER

Last changed (administrative field for updating): 3/08/02 by ToxWorks

17) TOXICITY TO REPRODUCTION

TEST SUBSTANCE

Identity: Propylene Carbonate

METHOD

Method/guideline followed: Assessment of reproductive organs in a 14 week study
Type (one generation, two generation, etc.): Assessment of reproductive organs in a 14 week study
GLP (Y/N): Yes
Year (study performed): 1991
Species: Rat
Strain: Harlan F344
Route of administration - oral (gavage, drinking water, feed), dermal, inhalation (aerosol, vapor, gas, particulate), other: Aerosol inhalation
Doses/concentration levels: 0, 100, 500, 1000 mg/m^3, diameter MMAD) = 4.9 +/- 2.5 gsd
Sex: Both
Control group and treatment: Clean air
Frequency of treatment: 93 Days
Statistical methods: One-way analysis of variance, followed by Dunnett's or Tukey's tests
Remarks field for Test Conditions:
- Test animals:
· Number, age, sex per dose for P, F1 and F2, if appropriate: 10 per sex per group, 47 days old
- Test design:
· Vehicle: None
- Parameters assessed during study P and F1 as appropriate:
· Clinical observations performed and frequency (clinical pathology, functional observations, etc.): Daily
· Estrous cycle length and pattern (number of days spent in each phase): Not assessed
· Sperm examination (epididymal or vas sperm, concentration, motility, morphology): Not assessed
- Parameters assessed during study F1 and F2, as appropriate:
· Clinical observations performed and frequency (weight gain, growth rate, etc.): Weekly BW
· Organs examined at necropsy (macroscopic and microscopic): Ovaries, uterus, testes, accessory sex organs

RESULTS

NOAEL (NOEL) and LOAEL (LOEL) for P, F1 and F2, as appropriate: 100 mg/m^3
Actual dose received by dose level by sex if known
Parental data and F1 as appropriate (toxic response/effects with NOAEL value):
Periocular swelling seen in a few males at 500 and 1000 mg/m^3
Statistical results, as appropriate
Remarks field for Results:
- Body weight: No treatment effect
- Food/water consumption: No treatment effect
- Hematological findings incidence and severity: No treatment effect
- Clinical biochemistry findings incidence and severity: No treatment effect
- Mortality: No treatment effect
- Gross pathology incidence and severity: No treatment effect
- Organ weight changes: No treatment effect
· Histopathology incidence and severity: No effect on ovaries, testes or accessory sex organs

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter: The submitter concludes that propylene carbonate had no effect on reproductive organs

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 2, key study
Remarks field for Data Reliability: Not a guideline study of reproductive effects, but indicates no effects would be expected.

REFERENCES (Free Text)

Burleigh-Flayer, H.D., Nachreiner, D.J., Kintigh, W.J., 1991. Propylene carbonate: Fourteen-Week aerosol inhalation study on rats with neurotoxicity evaluation. Bushy Run Research Center Final Report 52-637, pp. 1 – 56, plus 12 appendices.

OTHER

Last changed (administrative field for updating): 3/08/02 by ToxWorks

18) DEVELOPMENTAL TOXICITY/TERATOGENICITY

TEST SUBSTANCE

Identity: Propylene carbonate

METHOD

Method/guideline followed
GLP (Y/N): Yes
Year (study performed): 1988
Species: Rat
Strain: Charles River Sprague-Dawley
Route of administration - oral (gavage, drinking water, feed), dermal, inhalation (aerosol, vapor, gas, particulate), other: Oral (gavage)
Doses/concentration levels: 0, 1000, 3000 and 5000 mg/kg/day
Sex: Females
Exposure period: Days 6-15 of gestation
Frequency of treatment: Once per day
Control group and treatment: Distilled water by gavage
Duration of test: Days 6-20 of gestation
Statistical methods: Anova, followed by Dunnett's
Remarks field for Test Conditions:
- Age at study initiation: 80-120 days
- Number of animals per dose per sex: 27
- Vehicle: None
- Clinical observations performed and frequency : Daily
- Mating procedures (M/F ratios per cage, length of cohabitation, proof of pregnancy): One male with one or two females until signs of copulation
- Parameters assessed during study (maternal and fetal): Daily toxicologic signs; body weight days 6, 9, 12, 15, 20; and food consumption days 0-6, 6-13, 13-20.
- Organs examined at necropsy (macroscopic and microscopic): Complete necropsy; number and location of viable fetuses, early and late resorptions, total implantations and corpora lutea, half of fetuses soft tissue analysis, other half skeletal analysis.

RESULTS

NOAEL (NOEL) and LOAEL (LOEL) maternal toxicity: 1000 mg/kg/day
NOAEL (NOEL) and LOAEL (LOEL) developmental toxicity: 5000 mg/kg/day
Actual dose received by dose level by sex if available
Maternal data with dose level (with NOAEL value). Provide at a minimum qualitative descriptions of responses where dose related effects were seen. Mortality, salivation, decreased activity, abnormal gait, dyspnea, cyanosis
Fetal data with dose level (with NOAEL value). Provide at a minimum qualitative descriptions of responses where dose related effects were seen. No effects
Statistical results, as appropriate
Remarks for Results:
- Mortality and day of death: at 3000 mg//kg/day: days 9 and 13; at 5000 mg/kg/day: days 10, 10, 11, 11, 14
- Number pregnant per dose level: At cesarean section, 27, 26, 23, 22 pregnant at 0, 1000, 3000 and 5000 mg/kg/day
- Number aborting: None

- Number of implantations:		15.4	15.2	15.6	14.9
- Pre and post implantation loss, if available:	pre (%):	8.0	6.3	10.2	10.6
	post (%)	4.7	9.7	5.2	11.7
- Number of corpora lutea (recommended):		17.0	16.3	17.5	16.6

- Duration of Pregnancy: Terminated day 20 of gestation
- Body weight: Decreased body weight gain at 5000 mg/kg/day: 53 g vs 77 g in control days 6-15
- Food/water consumption: Reduced food consumption at 3000 and 5000 mg/kg/day days 6-13
- Description, severity, time of onset and duration of clinical signs: Salivation, in some rats days 6-15, decreased activity in some rats days 6-15 at 3000 and 5000 mg/k/day
- Hematological findings incidence and severity: Not examined
- Clinical biochemistry findings incidence and severity: Not examined
- Gross pathology incidence and severity: No adverse effects
- Organ weight changes, particularly effects on total uterine weight: Not examined
- Histopathology incidence and severity: Not examined
- Fetal data, provide at a minimum qualitative descriptions of responses where dose related effects were seen

· Litter size and weights:	size	14.6	13.6	14.7	13.2
	weight	3.8	3.9	3.8	3.6
· Number viable (number alive and number dead)					
· Sex ratio:	% male	53	48	51	50

· Grossly visible abnormalities, external, soft tissue and skeletal abnormalities: No significant differences

CONCLUSIONS

Remarks field with the ability to identify source of comment, i.e. author and/or submitter. Submitter concludes that propylene carbonate does not induce developmental effects.

DATA QUALITY

Reliabilities (Klimisch Code, if used, possibly a flag if 'key study'): 1, key study

REFERENCES (Free Text)

Margitich, D.J. (1988). Developmental toxicity study in rats. Pharmakon Research International, Inc. Final Report PH 328-TX-001-88, pp. 1-44, plus 2 appendices.

OTHER

Last changed (administrative field for updating): 3/11/02 by ToxWorks